

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



56

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C12N 15/12, 15/62, 5/10, C07K 14/705, 16/28, C12Q 1/68, A61K 38/17, 31/70, 48/00		A2	(11) International Publication Number: WO 00/06733 (43) International Publication Date: 10 February 2000 (10.02.00)
(21) International Application Number: PCT/US99/17309 (22) International Filing Date: 29 July 1999 (29.07.99) (30) Priority Data: 60/094,506 29 July 1998 (29.07.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application 60/094,506 (CIP) US Filed on 29 July 1998 (29.07.98) (71) Applicant (for all designated States except US): HESKA CORPORATION [US/US]; 1825 Sharp Point Drive, Fort Collins, CO 80525 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): SIM, Gek-Kee [US/US]; 3622 Terry Point Drive, Fort Collins, CO 80524 (US). DREITZ, Matthew, J. [US/US]; 4324 Winterstone, Fort Collins, CO 80525 (US). (74) Agents: CONNELL, Gary, J. et al.; Sheridan Ross P.C., Suite 3500, 1700 Lincoln Street, Denver, CO 80203-4501 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(54) Title: T CELL RECEPTOR PROTEINS, NUCLEIC ACID MOLECULES, AND USES THEREOF			
(57) Abstract <p>The present invention relates to TCR $V\beta$ proteins; to TCR $V\beta$ nucleic acid molecules, including those that encode such TCR-$V\beta$ proteins; to antibodies raised against such TCR $V\beta$ proteins; and to therapeutic compounds that regulate TCR $V\beta$ function. The present invention also includes methods to identify and obtain such proteins, nucleic acid molecules, antibodies, and inhibitory compounds. Also included in the present invention are therapeutic compositions comprising such proteins, nucleic acid molecules, antibodies and/or inhibitory compounds as well as the use of such therapeutic compositions to regulate an immune response in an animal. Also included in the present invention are methods to detect T cell expansion in an animal using reagents including, or derived from such proteins, nucleic acid molecules or antibodies.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

"T CELL RECEPTOR PROTEINS, NUCLEIC ACID MOLECULES,
AND USES THEREOF "

FIELD OF THE INVENTION

The present invention relates to T cell receptor beta chain variable region nucleic
5 acid molecules, proteins encoded by such nucleic acid molecules, antibodies raised
against such proteins and inhibitors of such proteins or nucleic acid molecules. The
present invention also includes therapeutic compositions comprising such nucleic acid
molecules, proteins, antibodies and/or inhibitors, as well as their use to regulate an
immune response in an animal.

10 BACKGROUND OF THE INVENTION

The immune system of an animal is characterized by its ability to respond to a
diverse set of antigenic determinants, or epitopes. This response is reflected through T
and B lymphocytes, also referred to as T cells and B cells, respectively. The immune
system, comprising these specialized cells, recognizes and processes foreign pathogens
15 and macromolecules. Lymphocytes individually exhibit high specificity in recognition
of particular molecular structures of antigens. The structural properties are recognized
by T cell receptors, which act as antigen receptors.

T cell receptors (TCR) are members of the immunoglobulin superfamily. A
TCR molecule comprises two polypeptide chains, generally an alpha chain and a beta
20 chain. Each chain comprises an amino terminal variable region domain (V) and a
carboxyl terminal constant region domain (C), and can be designated with α or β when
indicating the particular chain of origin. V and C regions are encoded by V region or C
region genes, respectively. Each domain can be stabilized by a disulfide bond between
two conserved cysteine residue pairs on each chain. Each chain is anchored to the cell
25 membrane by a hydrophobic transmembrane domain, which typically spans the entire
lipid bilayer of the membrane. A short carboxyl domain extends into the cytoplasm.

The α and β chains of the TCR are encoded by gene segments analogous to the
variable region (V), the diversity region (D), the joining region (J) and the constant
region (C) of immunoglobulin genes. Diversity in the TCR repertoire arises, in part,

-2-

from the rearrangement of V, D and J regions and from the insertion of or deletion of nucleotides at the junction between the V, D and J regions.

Previous investigators have described TCR beta chain sequences, e.g., Malisson et al., *Cell*, vol. 37, pp. 1101-1110, 1984; Patten et al., *Nature*, vol. 312, pp. 40-46, 1984; Davis et al., *Nature*, vol. 334, pp. 395-402, 1988; Hood et al., U.S. Patent No. 4,886,743, issued Dec. 12, 1989; and Makrides et al., U.S. Patent No. 5,552,300, issued Sep. 3, 1996.

T cells play a pivotal role in the differentiation and regulation of immune cells. Previous investigators have studied diseases in which there appears to be improper immune regulation, such as autoimmunity and some forms of immunodeficiency, and have implicated T cells in the pathogenesis of such diseases. In addition, situations exist in which clonal or oligoclonal expansion of a particular T cell population, identified by the presence of a particular TCR, can be representative of a disease state. One example is the presence of malignancy which has resulted in a T cell leukemia or lymphoma (e.g., Hood et al., *ibid.*). In situations of T cell leukemias or lymphomas, a TCR acts as a unique tumor marker since the TCR is stably rearranged and presented on the surface of the cell.

In summary, there remains a need to develop methods and compounds useful for the detection and treatment of undesired immune responses involving T cells.

20

SUMMARY OF THE INVENTION

The present invention relates to T cell receptor nucleic acid molecules, proteins encoded by such nucleic acid molecules, antibodies raised against such proteins and inhibitors of such proteins or nucleic acid molecules. The present invention also includes therapeutic compositions comprising such nucleic acid molecules, proteins, antibodies and/or inhibitors, as well as their use to regulate an immune response in an animal. The present invention also includes methods to detect T cell expansion using reagents including or derived from such nucleic acid molecules, proteins and/or antibodies, as well as the use of such methods to diagnose abnormal states or disease in an animal.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 illustrates PCR amplified TCR V β DNA using DNA from tissue of normal dogs and dogs having lymphoma.

Figs. 2A, 2B and 2C illustrate fingerprints of TCR V β DNA from a normal dog.

5 Figs. 3A, 3B and 3C illustrate fingerprints of TCR V β DNA from a dog having lymphoma.

Fig. 4 illustrates a comparison between fingerprints of TCR V β DNA from a normal dog and a dog having lymphoma.

DETAILED DESCRIPTION OF THE INVENTION

10 The present invention provides for isolated T cell receptor beta chain variable region (TCR V β) proteins, isolated TCR V β nucleic acid molecules, antibodies directed against TCR V β proteins, and compounds derived therefrom that regulate the immune response of an animal. A TCR V β protein can refer to a TCR V β protein or a homolog thereof. As used herein, the term "TCR V β " refers to a molecule that can include the
15 variable (V) region, alone or in combination with the diversity (D) and/or joining (J) regions of a TCR beta chain. It is known to one of skill in the art that the size and sequence of V, D and J regions of a TCR beta chain can vary as a result of any given recombination event between genes encoding such V, D and J regions. Typical consensus sequences used to identify the junction between the V, D and J regions are
20 also known to one of skill in the art, thereby enabling the identification of the size and sequence of the V, D or J regions of a TCR beta chain from a novel nucleic acid or amino acid sequence. Compounds derived from TCR V β proteins or nucleic acid molecules of the present invention include compounds including at least a portion of, or designed using, such proteins or nucleic acid molecules.

25 As used herein, the phrase "regulate an immune response" refers to modulating the activity of cells involved in an immune response. The term "regulate" can refer to increasing or decreasing an immune response. Regulation of an immune response can be determined using methods known in the art as well as methods disclosed herein. As used herein, the terms isolated TCR V β proteins and isolated TCR V β nucleic acid
30 molecules refers to TCR V β proteins and TCR V β nucleic acid molecules derived from mammals, preferably canids, more preferably dogs, and, as such, can be obtained from

their natural source, or can be produced using, for example, recombinant nucleic acid technology or chemical synthesis. Also included in the present invention is the use of these proteins, nucleic acid molecules, antibodies, and compounds derived therefrom as therapeutic compositions to regulate the immune response of an animal as well as in
5 other applications, such as those disclosed below.

One embodiment of the present invention is an isolated protein that includes a TCR V β protein. It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, a protein refers to one or more proteins or at least one protein. As such, the terms "a" (or "an"), "one or more" and "at least one" can be used
10 interchangeably herein. It is also to be noted that the terms "comprising", "including", and "having" can be used interchangeably. According to the present invention, an isolated, or biologically pure, protein, is a protein that has been removed from its natural milieu. As such, "isolated" and "biologically pure" do not necessarily reflect the extent to which the protein has been purified. An isolated protein of the present invention can
15 be obtained from its natural source, can be produced using recombinant DNA technology, or can be produced by chemical synthesis.

As used herein, an isolated TCR V β protein of the present invention (i.e., a TCR V β protein) can be a full-length protein or any homolog of such a protein. Full-length proteins can refer to proteins having the V, D, J and C regions of a beta chain or
20 one or more of such regions. It is to be noted that the term "a homolog" refers to one or more or at least one homolog. An isolated protein of the present invention, including a homolog, can be identified in a straight-forward manner by the protein's ability to elicit an immune response against a TCR V β protein or to bind to a major histocompatibility (MHC) molecule or superantigen. Examples of TCR V β homologs include TCR V β
25 proteins in which amino acids have been deleted (e.g., a truncated version of the protein, such as a peptide), inserted, inverted, substituted and/or derivatized (e.g., by glycosylation, phosphorylation, acetylation, myristoylation, prenylation, palmitoylation, amidation and/or addition of glycerophosphatidyl inositol) such that the homolog includes at least one epitope capable of eliciting an immune response against a TCR V β
30 protein, and/or of binding to an antibody directed against a TCR V β protein. That is, when the homolog is administered to an animal as an immunogen, using techniques

-5-

known to those skilled in the art, the animal will produce an immune response against at least one epitope of a natural TCR V β protein. The ability of a protein to effect an immune response can be measured using techniques known to those skilled in the art. As used herein, the term "epitope" refers to the smallest portion of a protein or other antigen capable of selectively binding to the antigen binding site of an antibody. It is well accepted by those skilled in the art that the minimal size of a protein epitope is about six to seven amino acids. Other examples of TCR V β protein homologs include those homologs that are capable of binding to MHC, in the presence or absence of peptide, or superantigen. The ability of a protein to bind to MHC or superantigen can be measured using various methods well known to those of skill in the art.

TCR V β protein homologs can be the result of natural allelic variation or natural mutation. TCR V β protein homologs of the present invention can also be produced using techniques known in the art including, but not limited to, direct modifications to the protein or modifications to the gene encoding the protein using, for example, classic or recombinant DNA techniques to effect random or targeted mutagenesis.

TCR V β proteins of the present invention are encoded by TCR V β nucleic acid molecules. As used herein, a TCR V β nucleic acid molecule includes nucleic acid sequences related to a natural TCR V β gene. It is to be noted that the term "a nucleic acid molecule", "a gene" or "a nucleic acid sequence" refers to one or more or at least one nucleic acid molecule, gene or nucleic acid sequence, respectively. As used herein, a TCR V β gene includes all regions of the gene such as regulatory regions that control production of the TCR V β protein encoded by the gene (such as, but not limited to, transcription, translation or post-translation control regions) as well as the coding region itself, and any introns or non-translated coding regions. As used herein, a gene that "includes" or "comprises" a sequence may include that sequence in one contiguous array, or may include the sequence as fragmented exons. As used herein, the term "coding region" refers to a continuous linear array of nucleotides that translates into a protein. A full-length coding region is that coding region that is translated into a full-length, i.e., a complete, protein as would be initially translated in its natural milieu, prior to any post-translational modifications.

In one embodiment, a TCR V β gene of the present invention includes the nucleic acid sequence SEQ ID NO:1, as well as the complement of SEQ ID NO:1. Nucleic acid sequence SEQ ID NO:1 represents the deduced sequence of the coding strand of a cDNA (complementary DNA) denoted herein as nucleic acid molecule nCaV β 3₃₈₁, the production of which is disclosed in the Examples. Nucleic acid molecule nCaV β 3₃₈₁ comprises the coding region for the V, D and J regions of TCRV β 3. (also referred to herein as hcV β 3). The complement of SEQ ID NO:1 (represented herein by SEQ ID NO:3) refers to the nucleic acid sequence of the strand complementary to the strand having SEQ ID NO:1, which can easily be determined by those skilled in the art. Likewise, a nucleic acid sequence complement of any nucleic acid sequence of the present invention refers to the nucleic acid sequence of the nucleic acid strand that is complementary to (i.e., can form a double helix with) the strand for which the sequence is cited. It should be noted that since nucleic acid sequencing technology is not entirely error-free, SEQ ID NO:1 (as well as other nucleic acid and protein sequences presented herein) represents an apparent nucleic acid sequence of the nucleic acid molecule encoding a TCR V β protein of the present invention.

In another embodiment, a TCR V β gene of the present invention includes the nucleic acid sequence SEQ ID NO:4, as well as the complement of SEQ ID NO:4 represented by SEQ ID NO:6. Nucleic acid sequence SEQ ID NO:4 represents the deduced sequence of the coding strand of a cDNA (complementary DNA) denoted herein as nucleic acid molecule nCaV β 4₄₀₈, the production of which is disclosed in the Examples. Nucleic acid molecule nCaV β 4₄₀₈ comprises the coding region for the V, D and J regions of TCRV β 4 (also referred to herein as hcV β 4).

In another embodiment, a TCR V β gene of the present invention includes the nucleic acid sequence SEQ ID NO:9, as well as the complement of SEQ ID NO:9 represented by SEQ ID NO:11. Nucleic acid sequence SEQ ID NO:9 represents the deduced sequence of the coding strand of a cDNA (complementary DNA) denoted herein as nucleic acid molecule nCaV β 12₄₀₈, the production of which is disclosed in the Examples. Nucleic acid molecule nCaV β 12₄₀₈ comprises the coding region for the V, D and J regions of TCRV β 12 (also referred to herein as hcV β 12).

- 7 -

In another embodiment, a TCR V β gene of the present invention includes the nucleic acid sequence SEQ ID NO:98, as well as the complement of SEQ ID NO:98 represented by SEQ ID NO:100. Nucleic acid sequence SEQ ID NO:98 represents the deduced sequence of the coding strand of a cDNA (complementary DNA) denoted
5 herein as nucleic acid molecule nCaV β 72₄₃₈, the production of which is disclosed in the Examples. Nucleic acid molecule nCaV β 72₄₃₈ comprises the coding region for the V, D, and J regions of TCRV β 72 (also referred to herein as hcV β 72).

In another embodiment, a TCR V β gene of the present invention includes the nucleic acid sequence SEQ ID NO:19, as well as the complement of SEQ ID NO:19
10 represented by SEQ ID NO:19. Nucleic acid sequence SEQ ID NO:19 represents the deduced sequence of the coding strand of a cDNA (complementary DNA) denoted herein as nucleic acid molecule nCaV β 21₄₆₂, the production of which is disclosed in the Examples. Nucleic acid molecule nCaV β 21₄₆₂ comprises the coding region for the V, D and J regions of TCRV β 21 (also referred to herein as hcV β 21).

15 In another embodiment, a TCR V β gene of the present invention includes the nucleic acid sequence SEQ ID NO:22, as well as the complement of SEQ ID NO:22 represented by SEQ ID NO:22. Nucleic acid sequence SEQ ID NO:22 represents the deduced sequence of the coding strand of a cDNA (complementary DNA) denoted herein as nucleic acid molecule nCaV β 54₄₁₇, the production of which is disclosed in the
20 Examples. Nucleic acid molecule nCaV β 54₄₁₇ comprises the coding region for the V, D and J regions of TCRV β 54 (also referred to herein as dtb54).

In another embodiment, a TCR V β gene of the present invention includes the nucleic acid sequence SEQ ID NO:25, as well as the complement of SEQ ID NO:25 represented by SEQ ID NO:25. Nucleic acid sequence SEQ ID NO:25 represents the
25 deduced sequence of the coding strand of a cDNA (complementary DNA) denoted herein as nucleic acid molecule nCaV β 182₄₂₃, the production of which is disclosed in the Examples. Nucleic acid molecule nCaV β 182₄₂₃ comprises the coding region for the V, D and J regions of TCRV β 182 (also referred to herein as dtb182).

In another embodiment, a TCR V β gene or nucleic acid molecule can be an
30 allelic variant that includes a similar but not identical sequence to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:11, SEQ ID

NO:98, SEQ ID NO:100, or any other TCR V β nucleic acid sequence cited herein. An allelic variant of a TCR V β nucleic acid molecule including SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:98 and SEQ ID NO:100, is a nucleic acid molecule that occurs at essentially the same locus
5 (or loci) in the genome as the nucleic acid molecule including SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:98 and SEQ ID NO:100, but which, due to natural variations caused by, for example, mutation or recombination, has a similar but not identical sequence. Because natural selection typically selects against alterations that affect function, allelic variants usually
10 encode proteins having similar activity to that of the protein encoded by the gene to which they are being compared. Allelic variants of genes or nucleic acid molecules can also comprise alterations in the 5' or 3' untranslated regions of the gene (e.g., in regulatory control regions), or can involve alternative splicing of a nascent transcript, thereby bringing alternative exons into juxtaposition. Allelic variants are well known to
15 those skilled in the art and would be expected to be found within a given genome, since the respective genomes are diploid, and sexual reproduction will result in the reassortment of alleles.

In one embodiment of the present invention, an isolated TCR V β protein is encoded by a nucleic acid molecule that hybridizes under stringent hybridization
20 conditions to a gene encoding a TCR V β protein (i.e., to a TCR V β gene). The minimal size of a TCR V β protein of the present invention is a size sufficient to be encoded by a nucleic acid molecule capable of forming a stable hybrid (i.e., hybridize under stringent hybridization conditions) with the complementary sequence of a nucleic acid molecule encoding the corresponding natural protein. The size of a nucleic acid molecule
25 encoding such a protein is dependent on the nucleic acid composition and the percent homology between the TCR V β nucleic acid molecule and the complementary nucleic acid sequence. It can easily be understood that the extent of homology required to form a stable hybrid under stringent conditions can vary depending on whether the homologous sequences are interspersed throughout a given nucleic acid molecule or are
30 clustered (i.e., localized) in distinct regions on a given nucleic acid molecule.

Stringent hybridization conditions are determined based on defined physical properties of the gene to which the nucleic acid molecule is being hybridized, and can be defined mathematically. Stringent hybridization conditions are those experimental parameters that allow an individual skilled in the art to identify significant similarities
5 between heterologous nucleic acid molecules. These conditions are well known to those skilled in the art. See, for example, Sambrook, *et al.*, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Labs Press, and Meinkoth, *et al.*, 1984, *Anal. Biochem.* 138, 267-284. As explained in detail in the cited references, the determination of hybridization conditions involves the manipulation of a set of variables including the
10 ionic strength (expressed as molarity (M), in moles/liter), the hybridization temperature (°C), the concentration of nucleic acid helix destabilizing agents (such as formamide), the average length of the shortest hybrid duplex (n), and the percent G + C composition of the fragment to which an unknown nucleic acid molecule is being hybridized. For nucleic acid molecules longer than about 50 nucleotides, these variables are inserted into
15 a standard mathematical formula to calculate the melting temperature, or T_m , of a given nucleic acid molecule. As defined in the formula below, T_m is the temperature at which two complementary nucleic acid molecule strands will disassociate, assuming 100% complementarity between the two strands:

$$T_m = 81.5^\circ\text{C} + 16.6 \log M + 0.41(\% \text{ G} + \text{C}) - 500/n - 0.61(\% \text{ formamide}).$$

20 For nucleic acid molecules smaller than about 50 nucleotides, hybrid stability is defined by the dissociation temperature (T_d), which is defined as the temperature at which 50% of the duplexes dissociate. For these smaller molecules, the stability at a standard ionic strength is defined by the following equation:

$$T_d = 4(\text{G} + \text{C}) + 2(\text{A} + \text{T}).$$

25 A temperature of 5°C below T_d is used to detect hybridization between perfectly matched molecules.

Also well known to those skilled in the art is how base-pair mismatch, i.e. differences between two nucleic acid molecules being compared, including non-complementarity of bases at a given location, and gaps due to insertion or deletion of
30 one or more bases at a given location on either of the nucleic acid molecules being compared, will affect T_m or T_d for nucleic acid molecules of different sizes. For

-10-

example, T_m decreases about 1°C for each 1% of mismatched base-pairs for hybrids greater than about 150 bp, and T_d decreases about 5°C for each mismatched base-pair for hybrids below about 50 bp. Conditions for hybrids between about 50 and about 150 base-pairs can be determined empirically and without undue experimentation using standard laboratory procedures well known to those skilled in the art. These simple procedures allow one skilled in the art to set the hybridization conditions (by altering, for example, the salt concentration, the formamide concentration or the temperature) so that only nucleic acid hybrids with greater than a specified % base-pair mismatch will hybridize. Stringent hybridization conditions are commonly understood by those skilled in the art to be those experimental conditions that will allow about 30% base-pair mismatch (i.e., about 70% identity). Because one skilled in the art can easily determine whether a given nucleic acid molecule to be tested is less than or greater than about 50 nucleotides, and can therefore choose the appropriate formula for determining hybridization conditions, he or she can determine whether the nucleic acid molecule will hybridize with a given nucleic acid molecule under stringent hybridization conditions and similarly whether the nucleic acid molecule will hybridize under conditions designed to allow a desired amount of base pair mismatch.

Hybridization reactions are often carried out by attaching the nucleic acid molecule to be hybridized to a solid support such as a membrane, and then hybridizing with a labeled probe suspended in a hybridization solution. Examples of common hybridization reaction techniques include the well-known Southern and northern blotting procedures. Typically, the actual hybridization reaction is done under non-stringent conditions, i.e., at a lower temperature and/or a higher salt concentration, and then high stringency is achieved by washing the membrane in a solution with a higher temperature and/or lower salt concentration in order to achieve the desired stringency.

For example, if the skilled artisan wished to identify a nucleic acid molecule that hybridizes under stringent hybridization conditions with a specific or known canine nucleic acid molecule of about 150 bp in length, the following conditions could preferably be used. The average G + C content of canine DNA includes about 35%, about 36%, about 37%, about 38%, about 39%, about 41%, about 42%, about 43%, about 44%, about 45%, with about 40% being preferred. The unknown nucleic acid

-11-

molecules would be attached to a support membrane, and the specified 150 bp nucleic acid molecule would be labeled, e.g. with a radioactive tag. The hybridization reaction could be carried out in a solution comprising 2X SSC and 0% formamide, at a temperature of about 37°C (low stringency conditions). Solutions of differing concentrations of SSC can be made by one of skill in the art by diluting a stock solution of 20X SSC (175.3 gram NaCl and about 88.2 gram sodium citrate in 1 liter of water, pH 7) to obtain the desired concentration of SSC. In order to achieve high stringency hybridization, the skilled artisan would calculate the washing conditions required to allow up to 30% base-pair mismatch. For example, in a wash solution comprising 1X SSC and 0% formamide, the T_m of perfect hybrids would be about 80.8°C:

$$81.5^{\circ}\text{C} + 16.6 \log (.15\text{M}) + (0.41 \times 40) - (500/150) - (0.61 \times 0) = 80.8^{\circ}\text{C}.$$

Thus, to achieve hybridization with nucleic acid molecules having about 30% base-pair mismatch, hybridization washes would be carried out at a temperature of about 50.8°C. It is within the skill of one in the art to calculate the hybridization temperature based on the formulae and G/C content disclosed herein.

In one embodiment of the present invention, a preferred TCR V β nucleic acid molecule includes a nucleic acid molecule which has greater than about 50 base pairs and which hybridizes under conditions which preferably allow about 20% base pair mismatch, more preferably under conditions which allow about 15% base pair mismatch, more preferably under conditions which allow about 10% base pair mismatch and even more preferably under conditions which allow about 5% base pair mismatch with a nucleic acid molecule selected from the group consisting of SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, and/or the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70 or SEQ ID NO:71.

Another preferred TCR V β nucleic acid molecule of the present invention includes a nucleic acid molecule which has greater than about 150 base pairs and which hybridizes under conditions which preferably allow about 30% base pair mismatch,

-12-

more preferably under conditions which allow about 25% base pair mismatch, more preferably under conditions which allow about 20% base pair mismatch, more preferably under conditions which allow about 15% base pair mismatch, more preferably under conditions which allow about 10% base pair mismatch and even more preferably under
5 conditions which allow about 5% base pair mismatch with a nucleic acid molecule selected from the group consisting of SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, and/or the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID
10 NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70 or SEQ ID NO:71.

Another preferred TCR V β nucleic acid molecule of the present invention includes a nucleic acid molecule which has greater than about 200 base pairs
15 and which hybridizes under conditions which preferably allow about 30% base pair mismatch, more preferably under conditions which allow about 25% base pair mismatch, more preferably under conditions which allow about 20% base pair mismatch, more preferably under conditions which allow about 15% base pair mismatch, more preferably under conditions which allow about 10% base pair mismatch
20 and even more preferably under conditions which allow about 5% base pair mismatch with a nucleic acid molecule selected from the group consisting of SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:21, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, SEQ ID NO:42, and/or the complement of a nucleic acid molecule that encodes
25 a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73 or SEQ ID NO:74.

Another embodiment of the present invention includes a nucleic acid molecule
30 comprising at least about 150 base-pairs, wherein said molecule hybridizes, in a solution comprising 1X SSC and 0% formamide, at a temperature of about 49°C, to an isolated

-13-

nucleic acid molecule selected from the group consisting of SEQ ID NO:3, SEQ ID NO:30, the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61 or SEQ ID NO:62.

Another embodiment of the present invention includes a nucleic acid molecule
5 comprising at least about 150 base-pairs, wherein said molecule hybridizes, in a solution comprising 1X SSC and 0% formamide, at a temperature of about 56°C, to an isolated nucleic acid molecule selected from the group consisting of SEQ ID NO:5, SEQ ID NO:8, SEQ ID NO:33, the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:63, SEQ ID NO:64 or SEQ ID
10 NO:65. Another embodiment of the present invention includes a nucleic acid molecule comprising at least about 150 base-pairs, wherein said molecule hybridizes, in a solution comprising 1X SSC and 0% formamide, at a temperature of about 53°C, to an isolated nucleic acid molecule selected from the group consisting of SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:36, the complement of a nucleic acid molecule that encodes a
15 protein having an amino acid sequence including SEQ ID NO:66, SEQ ID NO:67 or SEQ ID NO:68. Another embodiment of the present invention includes a nucleic acid molecule comprising at least about 150 base-pairs, wherein said molecule hybridizes, in a solution comprising 1X SSC and 0% formamide, at a temperature of about 41°C, to an isolated nucleic acid molecule selected from the group consisting of SEQ ID NO:100,
20 SEQ ID NO:18, SEQ ID NO:39, the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:69, SEQ ID NO:70 or SEQ ID NO:71. Another embodiment of the present invention includes a nucleic acid molecule comprising at least about 150 base-pairs, wherein said molecule hybridizes, in a solution comprising 1X SSC and 0% formamide, at a temperature of
25 about 29°C, to an isolated nucleic acid molecule selected from the group consisting of SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:42, the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:72, SEQ ID NO:73 or SEQ ID NO:74.

Another embodiment of the present invention includes TCR V β proteins. A
30 preferred TCR V β protein includes a protein encoded by a nucleic acid molecule which has greater than about 50 base pairs and which hybridizes under conditions which

-14-

preferably allow about 20% base pair mismatch, more preferably under conditions which allow about 15% base pair mismatch, more preferably under conditions which allow about 10% base pair mismatch and even more preferably under conditions which allow about 5% base pair mismatch with a nucleic acid molecule selected from the group

5 consisting of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:20, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:41, SEQ ID NO:44, SEQ ID NO:47, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID

10 NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80.

Another preferred TCR V β protein of the present invention includes a protein encoded by a nucleic acid molecule which has greater than about 150 base pairs and

15 which hybridizes under conditions which preferably allow about 30% base pair mismatch, more preferably under conditions which allow about 25% base pair mismatch, more preferably under conditions which allow about 20% base pair mismatch, more preferably under conditions which allow about 15% base pair mismatch, more preferably under conditions which allow about 10% base pair mismatch

20 and even more preferably under conditions which allow about 5% base pair mismatch with a nucleic acid molecule selected from the group consisting of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:20, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:41, SEQ ID NO:44, SEQ ID NO:47, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID

25 NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80.

Another preferred TCR V β protein of the present invention includes a protein

30 encoded by a nucleic acid molecule which has greater than about 50 base pairs which is preferably about 80% identical, more preferably about 85% identical, more preferably

-15-

about 90% identical, and even more preferably about 95% identical to a nucleic acid molecule having the nucleic acid sequence SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, and/or the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70 or SEQ ID NO:71.

Yet another preferred TCR V β of the present invention includes a protein encoded by a nucleic acid molecule which has greater than about 150 base pairs which is preferably about 70% identical, more preferably about 75% identical, more preferably about 80% identical, more preferably about 85% identical, more preferably about 90% identical and even more preferably about 95% identical to a nucleic acid molecule having the nucleic acid sequence SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, and/or the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70 or SEQ ID NO:71.

Yet another preferred TCR V β of the present invention includes a protein encoded by a nucleic acid molecule which has greater than about 200 base pairs which is preferably about 70% identical, more preferably about 75% identical, more preferably about 80% identical, more preferably about 85% identical, more preferably about 90% identical and even more preferably about 95% identical to a nucleic acid molecule having the nucleic acid sequence SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:21, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, SEQ ID NO:42, and/or the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ

ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73 or SEQ ID NO:74.

The minimal size of such a nucleic acid molecule is typically at least about 12 to about 15 nucleotides in length if the nucleic acid molecule is GC-rich and at least about 15 to about 17 bases in length if the nucleic acid molecule is AT-rich. The minimal size of a nucleic acid molecule used to encode a TCR V β protein homolog of the present invention is from about 12 to about 18 nucleotides in length. Thus, the minimal size of a TCR V β protein homolog of the present invention is from about 4 to about 6 amino acids in length. There is no limit, other than a practical limit, on the maximal size of a nucleic acid molecule encoding a TCR V β protein or protein homolog because a nucleic acid molecule of the present invention can include a portion of a gene, an entire gene, or multiple genes. The preferred size of a protein encoded by a nucleic acid molecule of the present invention depends on whether a full-length, fusion, multivalent, or functional portion of such a protein is desired. As used herein, "fragments thereof" and "portions thereof" are intended to be used interchangeably, and have a minimal size as disclosed herein.

The minimal size of a protein or nucleic acid molecule of the present invention also can include a portion of a protein or nucleic acid molecule that is less than 100% identical to another protein or nucleic acid molecule, when determined using hybridization or computer alignment methods disclosed herein. For example, a fragment of a hcV β 3 protein of the present invention is at least about 15 residues, preferably 20 residues and more preferably 25 residues in length; a fragment of a hcV β 4 protein of the present invention is at least about 10 residues, preferably 15 residues and more preferably 20 residues in length; a fragment of a hcV β 12 protein of the present invention is at least about 11 residues, preferably 15 residues and more preferably 20 residues in length; a fragment of a hcV β 72 protein of the present invention is at least about 18 residues, preferably 25 residues and more preferably 30 residues in length; or a fragment of a hcV β 21 protein of the present invention is at least about 13 residues, preferably 20 residues and more preferably 25 residues in length. In addition, a nucleic acid molecule fragment of a hcV β 3 nucleic acid molecule of the present invention is at least about 33 nucleotides, preferably 35 nucleotides and more preferably 40 nucleotides in length; a

-17-

fragment of a hcV β 4 nucleic acid molecule of the present invention is at least about 21 nucleotides, preferably 25 nucleotides and more preferably 30 nucleotides in length; a fragment of a hcV β 12 nucleic acid molecule of the present invention is at least about 19 nucleotides, preferably 25 nucleotides and more preferably 30 nucleotides in length; a
5 fragment of a hcV β 72 nucleic acid molecule of the present invention is at least about 27 nucleotides, preferably 30 nucleotides and more preferably 35 nucleotides in length; or a fragment of a hcV β 21 nucleic acid molecule of the present invention is at least about 176 nucleotides, preferably 180 nucleotides and more preferably 185 nucleotides in length.

- 10 Suitable protein fragments of the present invention include functional portions of a TCR V β protein of the present invention including, but not limited to, epitopes, MHC and/or peptide recognition sequences, antigen recognition sequences, superantigen recognition sequences, framework V regions and hypervariable V regions. Preferred functional portions of a TCR V β protein include the V, D or J regions. More preferred
15 functional portions of a TCR V β protein include: the putative signal peptide encoded by about nucleotide 1 to nucleotide 51, the V region encoded by about nucleotide 52 to about nucleotide 333, and the D/J region encoded by about nucleotide 334 to about nucleotide 381 of SEQ ID NO:1; the putative signal peptide encoded by nucleotide 25 to nucleotide 69, the V region encoded by nucleotide 70 to about nucleotide 351, and the
20 D/J region encoded by about nucleotide 352 to about nucleotide 408 of SEQ ID NO:4; the putative signal peptide encoded by nucleotide 7 to nucleotide 63, the V region encoded by nucleotide 64 to about nucleotide 339, and the D/J region encoded by about nucleotide 340 to about nucleotide 408 of SEQ ID NO:9; the putative signal peptide encoded by nucleotide 85 to nucleotide 141, the V region encoded by nucleotide 142 to
25 about nucleotide 423, and the D/J region encoded by about nucleotide 424 to about nucleotide 438 of SEQ ID NO:98; the putative signal peptide encoded by nucleotide 73 to nucleotide 114, the V region encoded by nucleotide 115 to about nucleotide 396, and the D/J region encoded by about nucleotide 397 to about nucleotide 462 of SEQ ID NO:19; the putative signal peptide encoded by nucleotide 13 to nucleotide 69, the V
30 region encoded by nucleotide 70 to about nucleotide 354, and the D/J region encoded by about nucleotide 355 to about nucleotide 417 of SEQ ID NO:22; and the putative signal

peptide encoded by nucleotide 40 to nucleotide 96, the V region encoded by nucleotide 97 to about nucleotide 369, and the D/J region encoded by about nucleotide 370 to about nucleotide 423 of SEQ ID NO:25.

It is known to those of skill in the art that the junction between the V and D
5 region can vary but that typically the carboxyl end of the V region contains one or more
of the amino acid residues alanine or serine following a cysteine. For example, one of
skill in the art would know that a conserved carboxyl V region sequence comprises the
amino acids CASS. Thus, a V region of the present invention can include the amino
acid sequence SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ
10 ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID
NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID
NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID
NO:79 or SEQ ID NO:80. The present invention includes nucleic acid molecules
having nucleic acid sequences encoding such proteins, which can be identified using the
15 nucleic acid sequences disclosed herein and standard codon usage known to those of
skill in the art; such as disclosed, for example, in Lehninger, *Biochemistry*, Worth
Publishers, Inc., 1975, which is incorporated herein by this reference in its entirety. For
example, a skilled artisan would know that codons encoding serine include ACA, ACC,
AGT, AGC or ACG, and codons that encode alanine include GCA, GCC, GCT or GCG.
20 One embodiment of a TCR V β protein of the present invention is a fusion
protein that includes a TCR V β protein-containing domain attached to one or more
fusion segments. It is to be noted that the term "a fusion protein" refers to one or more
or at least one fusion protein. Suitable fusion segments for use with the present
invention include, but are not limited to, segments that can: enhance a protein's stability;
25 deliver a TCR V β protein or portion thereof to a desired target; act as an
immunopotentiator to enhance an immune response against a TCR V β protein; and/or
assist in purification of a TCR V β protein (e.g., by affinity chromatography). A suitable
fusion segment can be a domain of any size that has the desired function (e.g., imparts
increased stability, imparts increased immunogenicity to a protein, and/or simplifies
30 purification of a protein). Fusion segments can be joined to amino and/or carboxyl
termini of the TCR V β -containing domain of the protein and can be susceptible to

-19-

cleavage in order to enable straight-forward recovery of a TCR V β protein. Fusion proteins are preferably produced by culturing a recombinant cell transformed with a fusion nucleic acid molecule that encodes a protein including the fusion segment attached to either the carboxyl and/or amino terminal end of a TCR V β -containing domain. Preferred fusion segments include a metal binding domain (e.g., a poly-histidine segment); an immunoglobulin binding domain (e.g., Protein A; Protein G; T cell; B cell; Fc receptor or complement protein antibody-binding domains); a sugar binding domain (e.g., a maltose binding domain); and/or a "tag" domain (e.g., at least a portion of -galactosidase, a strep tag peptide, a T7 tag peptide, a FlagTM peptide, or other domains that can be purified using compounds that bind to the domain, such as monoclonal antibodies). More preferred fusion segments include metal binding domains, such as a poly-histidine segment; a maltose binding domain; a strep tag peptide, such as that available from Biometra in Tampa, FL; and an S10 peptide. A preferred fusion protein of the present invention includes a TCR V β protein of the present invention linked to a TCR alpha chain in such a manner that the beta chain and alpha chain fold correctly to form a functional dimer. Another preferred fusion protein includes a TCR V β protein of the present invention linked to at least a portion of the constant region of an immunoglobulin in such a manner that crystallization of the V beta protein is enhanced by the presence of the immunoglobulin sequence.

20 Preferably a TCR V β protein of the present invention is isolated (including isolation of the natural protein or production of the protein by recombinant or synthetic techniques) from canids.

A preferred isolated protein of the present invention is an isolated protein that is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions with a gene comprising a nucleic acid sequence including SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:21, SEQ ID NO:24, SEQ ID NO:27, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, SEQ ID NO:42, SEQ ID NO:45, SEQ ID NO:48, a complement of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including

SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80.

A preferred isolated protein of the present invention is a protein encoded by at least one of the following nucleic acid molecules: nCaV β 3₃₈₁, nCaV β 3₃₃₃, nCaV β 3₃₃₀, nCaV β 4₄₀₈, nCaV β 4₃₈₄, nCaV β 4₃₅₁, nCaV β 4₃₃₉, nCaV β 12₄₀₈, nCaV β 12₄₀₂, nCaV β 12₃₃₉, nCaV β 12₃₄₅, nCaV β 72₄₃₈, nCaV β 72₃₉₉, nCaV β 72₄₂₃, nCaV β 72₃₄₂, nCaV β 21₄₆₂, nCaV β 21₃₉₀, nCaV β 21₃₉₆, nCaV β 21₃₄₈, nCaV β 54₄₁₇, nCaV β 54₄₀₅, nCaV β 54₃₅₄, nCaV β 54₃₄₈, nCaV β 182₄₂₃, nCaV β 182₃₈₄, nCaV β 182₃₆₉ and/or nCaV β 182₃₂₇; fragments thereof; or allelic variants of any of these nucleic acid molecules. Another preferred isolated protein is encoded by a nucleic acid molecule having nucleic acid sequence SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:98, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:22, SEQ ID NO:25, SEQ ID NO:28, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:37, SEQ ID NO:40, SEQ ID NO:43, SEQ ID NO:46, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80; fragments thereof or an allelic variant of such a nucleic acid molecule.

Translation of SEQ ID NO:1, the coding strand of nCaV β 3₃₈₁, yields a TCR V β protein of about 127 amino acids containing the beta chain V, D, and J regions, denoted herein as PCaV β 3₁₂₇, the amino acid sequence of which is presented in SEQ ID NO:2, assuming an open reading frame having a first codon spanning from nucleotide 1 through nucleotide 3 of SEQ ID NO:1 and a last codon spanning from nucleotide 379 through nucleotide 381 of SEQ ID NO:1. The partial putative signal sequence extends from nucleotide 1 to nucleotide 51 of SEQ ID NO:1. The proposed mature protein (i.e.,

canine TCR V β protein from which the signal sequence has been cleaved), denoted herein as PCaV β 3₁₁₀, contains about 110 amino acids, extending from residue 18 through residue 127 of SEQ ID NO:2. The nucleic acid molecule encoding PCaV β 3₁₁₀ is denoted herein as nCaV β 3₃₃₀, extending from nucleotide 52 through nucleotide 381 of
5 SEQ ID NO:1.

Translation of SEQ ID NO:4, the coding strand of nCaV β 4₄₀₈, yields a protein of about 128 amino acids containing the beta chain V, D, and J regions, denoted herein as PCaV β 4₁₂₈, the amino acid sequence of which is presented in SEQ ID NO:5, assuming an open reading frame having an initiation codon spanning from nucleotide 25 through
10 nucleotide 27 of SEQ ID NO:4 and a last codon spanning from nucleotide 406 through nucleotide 408 of SEQ ID NO:4. The coding region encoding PCaV β 4₁₂₈ is presented herein as nCaV β 4₃₈₄, which has the nucleotide sequence SEQ ID NO:7 (the coding strand) and SEQ ID NO:8 (the complementary strand). The putative signal sequence extends from nucleotide 25 to nucleotide 69 of SEQ ID NO:4. The proposed mature
15 protein (i.e., canine TCR V β protein from which the signal sequence has been cleaved), denoted herein as PCaV β 4₁₁₃, contains about 113 amino acids, extending from residue 60 through residue 128 of SEQ ID NO:5. The nucleic acid molecule encoding PCaV β 4₁₁₃ is denoted herein as nCaV β 4₃₃₉, extending from nucleotide 70 through nucleotide 408 of SEQ ID NO:4.

20 Translation of SEQ ID NO:9, the coding strand of nCaV β 12₄₀₈, yields a protein of about 134 amino acids containing the beta chain V, D, and J regions, denoted herein as PCaV β 12₁₃₄, the amino acid sequence of which is presented in SEQ ID NO:10, assuming an open reading frame having an initiation codon spanning from nucleotide 7 through nucleotide 9 of SEQ ID NO:9 and a last codon spanning from nucleotide 406
25 through nucleotide 408 of SEQ ID NO:9. The coding region encoding PCaV β 12₁₃₄ is presented herein as nCaV β 12₄₀₂, which has the nucleotide sequence SEQ ID NO:12 (the coding strand) and SEQ ID NO:13 (the complementary strand). The putative signal sequence extends from nucleotide 7 to nucleotide 63 of SEQ ID NO:9. The proposed mature protein (i.e., canine TCR V β protein from which the signal sequence has been
30 cleaved), denoted herein as PCaV β 12₁₁₅, contains about 115 amino acids, extending from residue 20 through residue 134 of SEQ ID NO:10. The nucleic acid molecule

-22-

encoding PCaV β 12₁₁₅ is denoted herein as nCaV β 12₃₄₅, extending from nucleotide 64 through nucleotide 408 of SEQ ID NO:9.

Translation of SEQ ID NO:98, the coding strand of nCaV β 72₄₃₈, yields a protein of about 133 amino acids containing the beta chain V, D, and J regions, denoted herein as PCaV β 72₁₃₃, the amino acid sequence of which is presented in SEQ ID NO:15, assuming an open reading frame having an initiation codon spanning from nucleotide 85 through nucleotide 87 of SEQ ID NO:98 and a last codon spanning from nucleotide 481 through nucleotide 438 of SEQ ID NO:98. The coding region encoding PCaV β 72₁₃₃ is presented herein as nCaV β 72₃₉₉, which has the nucleotide sequence SEQ ID NO:17 (the coding strand) and SEQ ID NO:18 (the complementary strand). The putative signal sequence extends from nucleotide 85 to nucleotide 141 of SEQ ID NO:98. The proposed mature protein (i.e., canine TCR V β protein from which the signal sequence has been cleaved), denoted herein as PCaV β 72₁₁₄, contains about 114 amino acids, extending from residue 20 through residue 133 of SEQ ID NO:98. The nucleic acid molecule encoding PCaV β 72₁₁₄ is denoted herein as nCaV β 72₃₄₂, extending from nucleotide 142 through nucleotide 438 of SEQ ID NO:19.

Translation of SEQ ID NO:19, the coding strand of nCaV β 21₄₆₂, yields a protein of about 130 amino acids containing the beta chain V, D, and J regions, denoted herein as PCaV β 21₁₃₀, the amino acid sequence of which is presented in SEQ ID NO:20, assuming an open reading frame having an initiation codon spanning from nucleotide 73 through nucleotide 75 of SEQ ID NO:19 and a last codon spanning from nucleotide 460 through nucleotide 462 of SEQ ID NO:19. The coding region encoding PCaV β 21₁₃₀ is presented herein as nCaV β 21₃₉₀, which extends from nucleotide 73 to nucleotide 462 of SEQ ID NO:19. The putative signal sequence extends from nucleotide 73 to nucleotide 114 of SEQ ID NO:19. The proposed mature protein (i.e., canine TCR V β protein from which the signal sequence has been cleaved), denoted herein as PCaV β 21₁₁₆, contains about 116 amino acids, extending from residue 15 through residue 130 of SEQ ID NO:19. The nucleic acid molecule encoding PCaV β 21₁₁₆ is denoted herein as nCaV β 21₃₄₈, extending from nucleotide 115 through nucleotide 462 of SEQ ID NO:19.

Translation of SEQ ID NO:22, the coding strand of nCaV β 54₄₁₇, yields a protein of about 135 amino acids containing the beta chain V, D, and J regions, denoted herein

-23-

as PCaV β 54₁₃₅, the amino acid sequence of which is presented in SEQ ID NO:23, assuming an open reading frame having an initiation codon spanning from nucleotide 13 through nucleotide 15 of SEQ ID NO:22 and a last codon spanning from nucleotide 415 through nucleotide 417 of SEQ ID NO:22. The coding region encoding PCaV β 54₁₃₅ is presented herein as nCaV β 54₄₀₅, which extends from nucleotide 13 to nucleotide 417 of SEQ ID NO:22. The putative signal sequence extends from nucleotide 13 to nucleotide 69 of SEQ ID NO:22. The proposed mature protein (i.e., canine TCR V β protein from which the signal sequence has been cleaved), denoted herein as PCaV β 54₁₁₆, contains about 116 amino acids, extending from residue 20 through residue 135 of SEQ ID NO:22. The nucleic acid molecule encoding PCaV β 54₁₁₆ is denoted herein as nCaV β 54₃₄₈, extending from nucleotide 70 through nucleotide 417 of SEQ ID NO:22.

Translation of SEQ ID NO:25, the coding strand of nCaV β 182₄₂₃, yields a protein of about 128 amino acids containing the beta chain V, D, and J regions, denoted herein as PCaV β 182₁₂₈, the amino acid sequence of which is presented in SEQ ID NO:26, assuming an open reading frame having an initiation codon spanning from nucleotide 40 through nucleotide 43 of SEQ ID NO:25 and a last codon spanning from nucleotide 421 through nucleotide 423 of SEQ ID NO:25. The coding region encoding PCaV β 182₁₂₈ is presented herein as nCaV β 182₃₈₄, which extends from nucleotide 40 to nucleotide 423 of SEQ ID NO:25. The putative signal sequence extends from nucleotide 40 to nucleotide 96 of SEQ ID NO:25. The proposed mature protein (i.e., canine TCR V β protein from which the signal sequence has been cleaved), denoted herein as PCaV β 182₁₀₉, contains about 109 amino acids, extending from residue 20 through residue 128 of SEQ ID NO:25. The nucleic acid molecule encoding PCaV β 182₁₀₉ is denoted herein as nCaV β 182₃₂₇, extending from nucleotide 97 through nucleotide 423 of SEQ ID NO:25.

Translation of SEQ ID NO:28, the coding strand of nCaV β 3₃₃₃, yields a protein of about 111 amino acids containing the beta chain V region, denoted herein as PCaV β 3₁₁₁, the amino acid sequence of which is presented in SEQ ID NO:29, assuming an open reading frame having a first codon spanning from nucleotide 1 through nucleotide 3 of SEQ ID NO:28 and a last codon spanning from nucleotide 331 through

-24-

nucleotide 333 of SEQ ID NO:28. The complement of SEQ ID NO:28 is SEQ ID NO:30.

Translation of SEQ ID NO:31, the coding strand of nCaV β 4₃₅₁, yields a protein of about 109 amino acids containing the beta chain V region, denoted herein as

- 5 PCaV β 4₁₀₉, the amino acid sequence of which is presented in SEQ ID NO:32, assuming an open reading frame having a first codon spanning from nucleotide 25 through nucleotide 27 of SEQ ID NO:31 and a last codon spanning from nucleotide 349 through nucleotide 351 of SEQ ID NO:31. The complement of SEQ ID NO:31 is SEQ ID NO:33.

- 10 Translation of SEQ ID NO:34, the coding strand of nCaV β 12₃₃₉, yields a protein of about 111 amino acids containing the beta chain V region, denoted herein as PCaV β 12₁₁₁, the amino acid sequence of which is presented in SEQ ID NO:35, assuming an open reading frame having a first codon spanning from nucleotide 7 through nucleotide 9 of SEQ ID NO:34 and a last codon spanning from nucleotide 337 through
15 nucleotide 339 of SEQ ID NO:34. The complement of SEQ ID NO:34 is SEQ ID NO:35.

Translation of SEQ ID NO:37, the coding strand of nCaV β 72₄₂₃, yields a protein of about 113 amino acids containing the beta chain V region, denoted herein as PCaV β 72₁₁₃, the amino acid sequence of which is presented in SEQ ID NO:38, assuming
20 an open reading frame having a first codon spanning from nucleotide 85 through nucleotide 87 of SEQ ID NO:37 and a last codon spanning from nucleotide 421 through nucleotide 423 of SEQ ID NO:37. The complement of SEQ ID NO:37 is SEQ ID NO:39.

- Translation of SEQ ID NO:40, the coding strand of nCaV β 21₃₉₆, yields a protein
25 of about 108 amino acids containing the beta chain V region, denoted herein as PCaV β 21₁₀₈, the amino acid sequence of which is presented in SEQ ID NO:41, assuming an open reading frame having a first codon spanning from nucleotide 73 through nucleotide 75 of SEQ ID NO:40 and a last codon spanning from nucleotide 394 through nucleotide 396 of SEQ ID NO:40. The complement of SEQ ID NO:40 is SEQ ID
30 NO:42.

-25-

Translation of SEQ ID NO:43, the coding strand of nCaV β 54₃₅₄, yields a protein of about 114 amino acids containing the beta chain V region, denoted herein as PCaV β 54₁₁₄, the amino acid sequence of which is presented in SEQ ID NO:44, assuming an open reading frame having a first codon spanning from nucleotide 13 through

5 nucleotide 15 of SEQ ID NO:43 and a last codon spanning from nucleotide 352 through nucleotide 354 of SEQ ID NO:43. The complement of SEQ ID NO:43 is SEQ ID NO:45.

Translation of SEQ ID NO:46, the coding strand of nCaV β 182₃₆₉, yields a protein of about 110 amino acids containing the beta chain V region, denoted herein as PCaV β 182₁₁₀, the amino acid sequence of which is presented in SEQ ID NO:47,

10 assuming an open reading frame having a first codon spanning from nucleotide 40 through nucleotide 42 of SEQ ID NO:46 and a last codon spanning from nucleotide 367 through nucleotide 369 of SEQ ID NO:46. The complement of SEQ ID NO:46 is SEQ ID NO:48.

Preferred TCR V β proteins of the present invention include proteins that are at

15 least about 65%, preferably at least about 70%, even more preferably at least about 75%, and even more preferably at least about 80% identical to PCaV β 3₁₂₇; are at least about 69%, preferably at least about 75%, even more preferably at least about 80%, and even more preferably at least about 85% identical to PCaV β 4₁₂₈; are at least about 57%, preferably at least about 60%, even more preferably at least about 65%, and even more

20 preferably at least about 70% identical to PCaV β 12₁₃₄; are at least about 65%, preferably at least about 70%, even more preferably at least about 75%, and even more preferably at least about 80% identical to PCaV β 72₁₃₃; or are at least about 60%, preferably at least about 65%, even more preferably at least about 70%, and even more preferably at least about 75% identical to PCaV β 21₁₃₀. More preferred are TCR V β proteins comprising

25 PCaV β 3₁₂₇, PCaV β 3₁₁₁, PCaV β 3₁₁₀, PCaV β 4₁₂₈, PCaV β 4₁₁₃, PCaV β 4₁₀₉, PCaV β 12₁₃₄, PCaV β 12₁₁₁, PCaV β 12₁₁₅, PCaV β 72₁₃₃, PCaV β 72₁₁₃, PCaV β 72₁₁₄, PCaV β 21₁₃₀, PCaV β 21₁₀₈, PCaV β 21₁₁₆, PCaV β 54₁₃₅, PCaV β 54₁₁₄, PCaV β 54₁₁₆, PCaV β 182₁₂₈, PCaV β 182₁₁₀, PCaV β 182₁₀₉ and fragments thereof; and proteins encoded by allelic variants of nucleic acid molecules encoding proteins PCaV β 3₁₂₇, PCaV β 3₁₁₁, PCaV β 3₁₁₀,

30 PCaV β 4₁₂₈, PCaV β 4₁₁₃, PCaV β 4₁₀₉, PCaV β 12₁₃₄, PCaV β 12₁₁₁, PCaV β 12₁₁₅, PCaV β 72₁₃₃, PCaV β 72₁₁₃, PCaV β 72₁₁₄, PCaV β 21₁₃₀, PCaV β 21₁₀₈, PCaV β 21₁₁₆,

-26-

PCaV β 54₁₃₅, PCaV β 54₁₁₄, PCaV β 54₁₁₆, PCaV β 182₁₂₈, PCaV β 182₁₁₀ and/or
PCaV β 182₁₀₉, and fragments thereof.

Other preferred TCR V β proteins of the present invention include proteins having amino acid sequences that are at least about 65%, preferably at least about 70%,
5 even more preferably at least about 75%, and even more preferably at least about 80% identical to SEQ ID NO:2; at least about 69%, preferably at least about 75%, even more preferably at least about 80%, and even more preferably at least about 85% identical to
SEQ ID NO:5; are at least about 57%, preferably at least about 60%, even more preferably at least about 65%, and even more preferably at least about 70% identical to
10 SEQ ID NO:10; are at least about 65%, preferably at least about 70%, even more preferably at least about 75%, and even more preferably at least about 80% identical to
SEQ ID NO:15; or are at least about 60%, preferably at least about 65%, even more preferably at least about 70%, and even more preferably at least about 75% identical to
SEQ ID NO:20. More preferred are TCR V β proteins comprising amino acid sequences
15 SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:20, SEQ ID
NO:23, SEQ ID NO:26, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID
NO:38, SEQ ID NO:41, SEQ ID NO:44, SEQ ID NO:47, SEQ ID NO:60, SEQ ID
NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID
NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID
20 NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID
NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80 and/or proteins
encoded by the complement of a nucleic acid sequence including SEQ ID NO:50, SEQ
ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID
NO:56; and TCR V β proteins encoded by allelic variants of nucleic acid molecules
25 encoding TCR V β proteins having amino acid sequences SEQ ID NO:2, SEQ ID NO:5,
SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:20, SEQ ID NO:23, SEQ ID NO:26, SEQ
ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:41, SEQ ID
NO:44, SEQ ID NO:47, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID
NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID
30 NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID
NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID

NO:78, SEQ ID NO:79, SEQ ID NO:80 and/or proteins encoded by the complement of a nucleic acid sequence including SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56; and fragments of any of such amino acid sequences.

- 5 A preferred isolated protein of the present invention comprises a protein selected from the group consisting of:(a) an isolated protein having an amino acid sequence that is at least about 55 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:29, SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 amino acids in length; (b) an
- 10 isolated protein having an amino acid sequence that is at least about 75 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:32, SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 15 amino acids in length; (c) an isolated protein having an amino acid sequence that is at least about 50% identical to an amino acid sequence selected from the
- 15 group consisting of SEQ ID NO:10, SEQ ID NO:35, SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 25 amino acids in length; and (d) an isolated protein having an amino acid sequence that is at least about 50% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:15, SEQ ID NO:38, SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a
- 20 fragment thereof that is at least about 35 amino acids in length.

- A preferred isolated protein of the present invention comprises a protein selected from the group consisting of:(a) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:28, SEQ ID NO:50, and a nucleic acid
- 25 sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 nucleotides in length; (b) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:31, SEQ ID NO:51, and
- 30 a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment that is

at least about 30 nucleotides in length; (c) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:34, SEQ ID NO:52, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 40 nucleotides in length; and (d) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:17, SEQ ID NO:37, SEQ ID NO:53, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 75 nucleotides in length.

It is known in the art that there are commercially available computer programs for determining the degree of similarity between two nucleic acid sequences. These computer programs include various known methods to determine the percentage identity and the number and length of gaps between hybrid nucleic acid molecules. Preferred methods to determine the percent identity among amino acid sequences and also among nucleic acid sequences include analysis using one or more of the commercially available computer programs designed to compare and analyze nucleic acid or amino acid sequences. These computer programs include, but are not limited to, GCGTM (available from Genetics Computer Group, Madison, WI), DNAsisTM (available from Hitachi Software, San Bruno, CA) and MacVectorTM (available from the Eastman Kodak Company, New Haven, CT). A preferred method to determine percent identity among amino acid sequences and also among nucleic acid sequences includes using the Compare function by maximum matching within the program DNAsis Version 2.1.

Additional preferred TCR V β proteins of the present invention include proteins encoded by nucleic acid molecules comprising at least a portion of nCaV β 3₃₈₁, nCaV β 3₃₃₃, nCaV β 3₃₃₀, nCaV β 4₄₀₈, nCaV β 4₃₈₄, nCaV β 4₃₅₁, nCaV β 4₃₃₉, nCaV β 12₄₀₈, nCaV β 12₄₀₂, nCaV β 12₃₃₉, nCaV β 12₃₄₅, nCaV β 72₄₃₈, nCaV β 72₃₉₉, nCaV β 72₄₂₃, nCaV β 72₃₄₂, nCaV β 21₄₆₂, nCaV β 21₃₉₀, nCaV β 21₃₉₆, nCaV β 21₃₄₈, nCaV β 54₄₁₇, nCaV β 54₄₀₅, nCaV β 54₃₅₄, nCaV β 54₃₄₈, nCaV β 182₄₂₃, nCaV β 182₃₈₄, nCaV β 182₃₆₉ and/or

-29-

nCaV β 182₃₂₇, fragments thereof, as well as TCR V β proteins encoded by allelic variants of such nucleic acid molecules.

Also preferred are TCR V β proteins encoded by nucleic acid molecules having nucleic acid sequences comprising at least a portion of SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:98, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:22, SEQ ID NO:25, SEQ ID NO:28, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:37, SEQ ID NO:40, SEQ ID NO:43, SEQ ID NO:46, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80, fragments thereof, as well as allelic variants of these nucleic acid molecules.

The present invention also includes mimetopes of TCR V β proteins of the present invention. As used herein, a mimetope of a TCR V β protein of the present invention refers to any compound that is able to mimic the activity of a TCR V β protein of the present invention, often because the mimetope has a structure that mimics the particular TCR V β protein. It is to be noted that the term "a mimetope" refers to one or more or at least one mimetope. Mimetopes can be, but are not limited to: peptides that have been modified to decrease their susceptibility to degradation such as all-D retro peptides; anti-idiotypic and/or catalytic antibodies, or fragments thereof; non-proteinaceous immunogenic portions of an isolated protein (e.g., carbohydrate structures); and synthetic or natural organic molecules, including nucleic acids. Such mimetopes can be designed using computer-generated structures of proteins of the present invention. Mimetopes can also be obtained by generating random samples of molecules, such as oligonucleotides, peptides, RNA or other organic molecules, non-organic molecules and screening such samples by affinity chromatography techniques using the corresponding binding partner.

-30-

Another embodiment of the present invention includes a TCR V β nucleic acid molecule. It is to be noted that the term "a nucleic acid molecule homolog" refers to one or more or at least one nucleic acid molecule homologs. In accordance with the present invention, an isolated nucleic acid molecule is a nucleic acid molecule that has been
5 removed from its natural milieu (i.e., that has been subjected to human manipulation) and can include DNA, RNA, or derivatives of either DNA or RNA. As such, "isolated" does not reflect the extent to which the nucleic acid molecule has been purified. An isolated TCR V β nucleic acid molecule of the present invention can be isolated from its natural source or produced using recombinant DNA technology (e.g., polymerase chain
10 reaction (PCR) amplification or cloning) or chemical synthesis. Isolated TCR V β nucleic acid molecules can include, for example, natural allelic variants and nucleic acid molecules modified by nucleotide insertions, deletions, substitutions, and/or inversions in a manner such that the modifications do not substantially interfere with the nucleic acid molecule's ability to encode a TCR V β protein of the present invention.

15 A nucleic acid molecule of the present invention can include one or more regulatory regions, full-length or partial coding regions, or combinations thereof. The minimal size of a nucleic acid molecule of the present invention is a size sufficient to allow the formation of a stable hybrid with the complementary sequence of another nucleic acid molecule. As such, the minimal size of a TCR V β nucleic acid molecule of
20 the present invention is from about 12 to about 18 nucleotides in length.

A TCR V β nucleic acid molecule homolog can be produced using a number of methods known to those skilled in the art, see, for example, Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Labs Press, *ibid.* For example, nucleic acid molecules can be modified using a variety of techniques
25 including, but not limited to, classic mutagenesis and recombinant DNA techniques such as site-directed mutagenesis, chemical treatment, restriction enzyme cleavage, ligation of nucleic acid fragments, PCR amplification, synthesis of oligonucleotide mixtures and ligation of mixture groups to "build" a mixture of nucleic acid molecules, and combinations thereof. Nucleic acid molecule homologs can be selected by hybridization
30 with a TCR V β nucleic acid molecule or by screening the function of a protein encoded

-31-

by the nucleic acid molecule (e.g., ability to elicit an immune response against at least one epitope of a TCR V β protein).

An isolated nucleic acid molecule of the present invention can include a nucleic acid sequence that encodes at least one TCR V β protein of the present invention, examples of such proteins being disclosed herein. Although the phrase "nucleic acid molecule" primarily refers to the physical nucleic acid molecule and the phrase "nucleic acid sequence" primarily refers to the sequence of nucleotides on the nucleic acid molecule, the two phrases can be used interchangeably, especially with respect to a nucleic acid molecule, or a nucleic acid sequence, being capable of encoding a TCR V β protein.

A preferred nucleic acid molecule of the present invention, when administered to an animal, is capable of regulating an immune response in an animal. As will be disclosed in more detail below, such a nucleic acid molecule can be, or encode, an antisense RNA, a molecule capable of triple helix formation, a ribozyme, or other nucleic acid-based drug compound. In additional embodiments, a nucleic acid molecule of the present invention can encode an immunoregulatory protein (e.g., a cell-bound or soluble TCR V β protein of the present invention), the nucleic acid molecule being delivered to the animal, for example, by direct injection (i.e., as a genetic vaccine) or in a vehicle such as a recombinant virus vaccine or a recombinant cell vaccine.

One embodiment of the present invention is a TCR V β nucleic acid molecule comprising all or part of nucleic acid molecules nCaV β 3₃₈₁, nCaV β 3₃₃₃, nCaV β 3₃₃₀, nCaV β 4₄₀₈, nCaV β 4₃₈₄, nCaV β 4₃₅₁, nCaV β 4₃₃₉, nCaV β 12₄₀₈, nCaV β 12₄₀₂, nCaV β 12₃₃₉, nCaV β 12₃₄₅, nCaV β 72₄₃₈, nCaV β 72₃₉₉, nCaV β 72₄₂₃, nCaV β 72₃₄₂, nCaV β 21₄₆₂, nCaV β 21₃₉₀, nCaV β 21₃₉₆, nCaV β 21₃₄₈, nCaV β 54₄₁₇, nCaV β 54₄₀₅, nCaV β 54₃₅₄, nCaV β 54₃₄₈, nCaV β 182₄₂₃, nCaV β 182₃₈₄, nCaV β 182₃₆₉ and/or nCaV β 182₃₂₇, or allelic variants of these nucleic acid molecules. Another preferred nucleic acid molecule comprises SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID

-32-

NO:36, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, a complement of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80, and complements thereof; as well as fragments thereof; as well as allelic variants of nucleic acid molecules having these nucleic acid sequences. Such nucleic acid molecules can include nucleotides in addition to those included in the SEQ ID NOs, such as, but not limited to, a full-length gene, a full-length coding region, a nucleic acid molecule encoding a fusion protein, or a nucleic acid molecule encoding a multivalent therapeutic compound.

In one embodiment, a TCR V β nucleic acid molecule of the present invention encodes a protein that is at least about 65%, preferably at least about 70%, even more preferably at least about 75%, and even more preferably at least about 80% identical to PCaV β 3₁₂₇; are at least about 69%, preferably at least about 75%, even more preferably at least about 80%, and even more preferably at least about 85% identical to PCaV β 4₁₂₈; are at least about 57%, preferably at least about 60%, even more preferably at least about 65%, and even more preferably at least about 70% identical to PCaV β 12₁₃₄; are at least about 65%, preferably at least about 70%, even more preferably at least about 75%, and even more preferably at least about 80% identical to PCaV β 72₁₃₃; or are at least about 60%, preferably at least about 65%, even more preferably at least about 70%, and even more preferably at least about 75% identical to PCaV β 21₁₃₀. Even more preferred is a nucleic acid molecule encoding PCaV β 3₁₂₇, PCaV β 3₁₁₁, PCaV β 3₁₁₀, PCaV β 4₁₂₈, PCaV β 4₁₁₃, PCaV β 4₁₀₉, PCaV β 12₁₃₄, PCaV β 12₁₁₁, PCaV β 12₁₁₅, PCaV β 72₁₃₃, PCaV β 72₁₁₃, PCaV β 72₁₁₄, PCaV β 21₁₃₀, PCaV β 21₁₀₈, PCaV β 21₁₁₆, PCaV β 54₁₃₅,

-33-

PCaV β 54₁₁₄, PCaV β 54₁₁₆, PCaV β 182₁₂₈, PCaV β 182₁₁₀ and/or PCaV β 182₁₀₉, fragments thereof, complements thereof, and/or an allelic variant of such a nucleic acid molecule.

In another embodiment, a TCR V β nucleic acid molecule of the present invention encodes a protein having an amino acid sequence that is at least about 65%,
 5 preferably at least about 70%, even more preferably at least about 75%, and even more preferably at least about 80% identical to SEQ ID NO:2; are at least about 69%, preferably at least about 75%, even more preferably at least about 80%, and even more preferably at least about 85% identical to SEQ ID NO:5; are at least about 57%, preferably at least about 60%, even more preferably at least about 65%, and even more
 10 preferably at least about 70% identical to SEQ ID NO:10; are at least about 65%, preferably at least about 70%, even more preferably at least about 75%, and even more preferably at least about 80% identical to SEQ ID NO:15; or at least about 60%, preferably at least about 65%, even more preferably at least about 70%, and even more preferably at least about 75% identical to SEQ ID NO:20. The present invention also
 15 includes a TCR V β nucleic acid molecule encoding a protein having at least a portion of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:20, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:41, SEQ ID NO:44, SEQ ID NO:47, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID
 20 NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80 and/or proteins encoded by the complement of a nucleic acid sequence including SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID
 25 NO:56; fragments thereof; complements thereof, as well as allelic variants of a TCR V β nucleic acid molecule encoding a protein having these sequences, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In one embodiment, a TCR V β nucleic acid molecule of the present invention is
 30 at least about 69%, preferably at least about 75%, even more preferably at least about 80%, and even more preferably at least about 85% identical to nCaV β 3₃₈₁; is at least

- 34 -

about 75%, preferably at least about 80%, even more preferably at least about 85%, and even more preferably at least about 90% identical to nCaV β 4₄₀₈; is at least about 72%, preferably at least about 80%, even more preferably at least about 85%, and even more preferably at least about 90% identical to nCaV β 12₄₀₈; is at least about 60%, preferably at least about 65%, even more preferably at least about 70%, and even more preferably at least about 75% identical to nCaV β 72₄₃₈; or is at least about 38%, preferably at least about 45%, even more preferably at least about 50%, and even more preferably at least about 55% identical to nCaV β 21₄₆₂. Even more preferred is a nucleic acid molecule comprising nCaV β 3₃₈₁, nCaV β 3₃₃₃, nCaV β 3₃₃₀, nCaV β 4₄₀₈, nCaV β 4₃₈₄, nCaV β 4₃₅₁, nCaV β 4₃₃₉, nCaV β 12₄₀₈, nCaV β 12₄₀₂, nCaV β 12₃₃₉, nCaV β 12₃₄₅, nCaV β 72₄₃₈, nCaV β 72₃₉₉, nCaV β 72₄₂₃, nCaV β 72₃₄₂, nCaV β 21₄₆₂, nCaV β 21₃₉₀, nCaV β 21₃₉₆, nCaV β 21₃₄₈, nCaV β 54₄₁₇, nCaV β 54₄₀₅, nCaV β 54₃₅₄, nCaV β 54₃₄₈, nCaV β 182₄₂₃, nCaV β 182₃₈₄, nCaV β 182₃₆₉ and/or nCaV β 182₃₂₇; fragments thereof; complements thereof; as well as an allelic variant of such a nucleic acid molecule.

In another embodiment, a TCR V β nucleic acid molecule of the present invention comprises a nucleic acid sequence that is at least about 69%, preferably at least about 75%, even more preferably at least about 80%, and even more preferably at least about 85% identical to SEQ ID NO:1; is at least about 75%, preferably at least about 80%, even more preferably at least about 85%, and even more preferably at least about 90% identical to SEQ ID NO:4; is at least about 72%, preferably at least about 80%, even more preferably at least about 85%, and even more preferably at least about 90% identical to SEQ ID NO:9; is at least about 60%, preferably at least about 65%, even more preferably at least about 70%, and even more preferably at least about 75% identical to SEQ ID NO:98; or is at least about 38%, preferably at least about 45%, even more preferably at least about 50%, and even more preferably at least about 55% identical to SEQ ID NO:19. The present invention also includes a TCR V β nucleic acid molecule comprising at least a portion of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:31, SEQ ID

-35-

NO:33, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, a complement of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80, and complements thereof; fragments thereof; complements thereof; as well as allelic variants of such TCR V β nucleic acid molecules, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

15 A preferred isolated nucleic acid molecule of the present invention comprises a nucleic acid sequence that hybridizes under stringent hybridization conditions to a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:21, SEQ ID NO:24, SEQ ID NO:27, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, SEQ ID NO:42, SEQ ID NO:45, SEQ ID NO:48, a complement of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80; or fragments thereof.

30 A preferred isolated nucleic acid molecule of the present invention comprises a nucleic acid sequence that is any of the following: (a) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group

-36-

consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:28, SEQ ID NO:30 and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 nucleotides in length; (b) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:31, SEQ ID NO:33, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 30 nucleotides in length; (c) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:34, SEQ ID NO:36, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 40 nucleotides in length; (d) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:37, SEQ ID NO:39, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 75 nucleotides in length; and (e) a nucleic acid sequence selected from the group consisting of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, and SEQ ID NO:56.

-37-

A preferred isolated nucleic acid molecule of the present invention comprises a nucleic acid sequence encoding a protein selected from the group consisting of: (a) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:28, SEQ ID NO:50, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 nucleotides in length; (b) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:31, SEQ ID NO:51, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 30 nucleotides in length; (c) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:34, SEQ ID NO:52, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 40 nucleotides in length; and (d) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:17, SEQ ID NO:37, SEQ ID NO:53, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 75 nucleotides in length.

Another embodiment of the present invention is an isolated nucleic acid molecule selected from the group consisting of: (a) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:28, and SEQ ID NO:30, or a fragment thereof, wherein said fragment has an at least a 20 contiguous nucleotide region identical in sequence to a 20 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:28, and SEQ ID NO:30; (b) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the

group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:31, and SEQ ID NO:33, or a fragment thereof, wherein said fragment has an at least a 25 contiguous nucleotide region identical in sequence to a 25 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:31 and SEQ ID NO:33; (c) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:34, and SEQ ID NO:36, or a fragment thereof, wherein said fragment has an at least a 30 contiguous nucleotide region identical in sequence to a 30 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:34, and SEQ ID NO:36; and (d) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:37, and SEQ ID NO:39, or a fragment thereof, wherein said fragment has an at least a 60 contiguous nucleotide region identical in sequence to a 60 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:37, and SEQ ID NO:39. The phrase, a homolog having an at least "x" contiguous nucleotide region identical in sequence to an "x" contiguous nucleotide region of a nucleic acid molecule selected from the group consisting of SEQ ID NO:"y", refers to an "x"-nucleotide in length nucleic acid molecule that is identical in sequence to an "x"-nucleotide portion of SEQ ID NO:"y", as well as to nucleic acid molecules that are longer in length than "x". The additional length may be in the form of nucleotides that extend from either the 5' or the 3' end(s) of the contiguous identical "x"-nucleotide portion. The 5' and/or 3' extensions can include one or more extensions that have no identity to an immunoregulatory molecule of the present invention, as well as extensions that show similarity or identity to cited nucleic acids sequences or portions thereof.

Knowing the nucleic acid sequences of certain TCR V β nucleic acid molecules of the present invention allows one skilled in the art to, for example, (a) make copies of those nucleic acid molecules, (b) obtain nucleic acid molecules including at least a

portion of such nucleic acid molecules (e.g., nucleic acid molecules including full-length genes, full-length coding regions, regulatory control sequences, truncated coding regions), and (c) obtain other TCR V β nucleic acid molecules. Such nucleic acid molecules can be obtained in a variety of ways including screening appropriate
5 expression libraries with antibodies of the present invention; traditional cloning techniques using oligonucleotide probes of the present invention to screen appropriate libraries; and PCR amplification of appropriate libraries or DNA using oligonucleotide primers of the present invention. Preferred libraries to screen or from which to amplify nucleic acid molecules include mammalian cDNA libraries as well as genomic DNA
10 libraries. Similarly, preferred DNA sources from which to amplify nucleic acid molecules include mammalian cDNA and genomic DNA. Techniques to clone and amplify genes are disclosed, for example, in Sambrook et al., *ibid*.

The present invention also includes nucleic acid molecules that are oligonucleotides capable of hybridizing, under stringent hybridization conditions, with
15 complementary regions of other, preferably longer, nucleic acid molecules of the present invention such as those comprising TCR V β nucleic acid molecules. Oligonucleotides of the present invention can be RNA, DNA, or derivatives of either. The minimum size of such oligonucleotides is the size required for formation of a stable hybrid between an oligonucleotide and a complementary sequence on a nucleic acid molecule of the present
20 invention. A preferred oligonucleotide of the present invention has a maximum size of about 100 nucleotides. A preferred oligonucleotide of the present invention has a minimum size of about 12 nucleotides. Preferably, an oligonucleotide of the present invention has a size from about 12 nucleotides to about 30 nucleotides and more preferably from about 15 nucleotides to about 25 nucleotides.

25 A preferred isolated oligonucleotide of the present invention comprises a unique nucleic acid sequence within a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ
30 ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID

-40-

NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, a complement of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80, and complements thereof; and a homolog thereof.

The present invention includes oligonucleotides that can be used, for example, as probes to identify nucleic acid molecules, primers to produce nucleic acid molecules, or therapeutic reagents to inhibit TCR V β protein production or activity (e.g., as antisense-, triplex formation-, ribozyme- and/or RNA drug-based reagents). The present invention also includes the use of such oligonucleotides to protect animals from disease using one or more of such technologies. Appropriate oligonucleotide-containing therapeutic compositions can be administered to an animal using techniques known to those skilled in the art.

Preferred oligonucleotides of the present invention include oligonucleotides comprising a unique nucleic acid sequence, as defined herein, within a nucleic acid molecule of the present invention or homologs thereof. Preferred homologs of an oligonucleotide are capable of priming a nucleic acid sequence.

One embodiment of the present invention includes a recombinant vector, which includes at least one isolated nucleic acid molecule of the present invention, inserted into any vector capable of delivering the nucleic acid molecule into a host cell. Such a vector contains heterologous nucleic acid sequences, that is nucleic acid sequences that are not naturally found adjacent to nucleic acid molecules of the present invention and that preferably are derived from a species other than the species from which the nucleic acid molecule(s) are derived. The vector can be either RNA or DNA, either prokaryotic or eukaryotic, and typically is a virus or a plasmid. Recombinant vectors can be used in the

-41-

cloning, sequencing, and/or otherwise manipulating of TCR V β nucleic acid molecules of the present invention.

One type of recombinant vector, referred to herein as a recombinant molecule, comprises a nucleic acid molecule of the present invention operatively linked to an expression vector. The phrase operatively linked refers to insertion of a nucleic acid molecule into an expression vector in a manner such that the molecule is able to be expressed when transformed into a host cell. As used herein, an expression vector is a DNA or RNA vector that is capable of transforming a host cell and of effecting expression of a specified nucleic acid molecule. Preferably, the expression vector is also capable of replicating within the host cell. Expression vectors can be either prokaryotic or eukaryotic, and are typically viruses or plasmids. Expression vectors of the present invention include any vectors that function (i.e., direct gene expression) in recombinant cells of the present invention, including in bacterial, fungal, parasite, insect, other animal, and plant cells. Preferred expression vectors of the present invention can direct gene expression in bacterial, yeast, insect and mammalian cells, and more preferably in the cell types disclosed herein

In particular, expression vectors of the present invention contain regulatory sequences such as transcription control sequences, translation control sequences, origins of replication, and other regulatory sequences that are compatible with the recombinant cell and that control the expression of nucleic acid molecules of the present invention. In particular, recombinant molecules of the present invention include transcription control sequences. Transcription control sequences are sequences which control the initiation, elongation, and termination of transcription. Particularly important transcription control sequences are those which control transcription initiation, such as promoter, enhancer, operator and repressor sequences. Suitable transcription control sequences include any transcription control sequence that can function in at least one of the recombinant cells of the present invention. A variety of such transcription control sequences are known to those skilled in the art. Preferred transcription control sequences include those which function in bacterial, yeast, helminth or other endoparasite, or insect and mammalian cells, such as, but not limited to, *tac*, *lac*, *trp*, *trc*, oxy-pro, omp/lpp, rrnB, bacteriophage lambda (such as lambda p_L and lambda p_R and

fusions that include such promoters), bacteriophage T7, T7 $_{lac}$, bacteriophage T3, bacteriophage SP6, bacteriophage SP01, metallothionein, alpha-mating factor, *Pichia* alcohol oxidase, alphavirus subgenomic promoter, antibiotic resistance gene, baculovirus, *Heliothis zea* insect virus, vaccinia virus, herpesvirus, raccoon poxvirus, other poxvirus, adenovirus, cytomegalovirus (such as immediate early promoter), simian virus 40, retrovirus, actin, retroviral long terminal repeat, Rous sarcoma virus, heat shock, phosphate and nitrate transcription control sequences as well as other sequences capable of controlling gene expression in prokaryotic or eukaryotic cells. Additional suitable transcription control sequences include tissue-specific promoters and enhancers as well as lymphokine-inducible promoters (e.g., promoters inducible by interferons or interleukins). Transcription control sequences of the present invention can also include naturally occurring transcription control sequences naturally associated with mammals, such as canine or feline transcription control sequences.

Suitable and preferred nucleic acid molecules to include in recombinant vectors of the present invention are as disclosed herein. Preferred nucleic acid molecules to include in recombinant vectors, and particularly in recombinant molecules, include nCaV β ₃₈₁, nCaV β ₃₃₃, nCaV β ₃₃₀, nCaV β ₄₀₈, nCaV β ₃₈₄, nCaV β ₃₅₁, nCaV β ₃₃₉, nCaV β ₁₂₄₀₈, nCaV β ₁₂₄₀₂, nCaV β ₁₂₃₃₉, nCaV β ₁₂₃₄₅, nCaV β ₇₂₄₃₈, nCaV β ₇₂₃₉₉, nCaV β ₇₂₄₂₃, nCaV β ₇₂₃₄₂, nCaV β ₂₁₄₆₂, nCaV β ₂₁₃₉₀, nCaV β ₂₁₃₉₆, nCaV β ₂₁₃₄₈, nCaV β ₅₄₄₁₇, nCaV β ₅₄₄₀₅, nCaV β ₅₄₃₅₄, nCaV β ₅₄₃₄₈, nCaV β ₁₈₂₄₂₃, nCaV β ₁₈₂₃₈₄, nCaV β ₁₈₂₃₆₉ and/or nCaV β ₁₈₂₃₂₇.

Recombinant molecules of the present invention may also (a) contain secretory signals (i.e., signal segment nucleic acid sequences) to enable an expressed TCR V β protein of the present invention to be secreted from the cell that produces the protein and/or (b) contain fusion sequences which lead to the expression of nucleic acid molecules of the present invention as fusion proteins. Examples of suitable signal segments include any signal segment capable of directing the secretion of a protein of the present invention. Preferred signal segments include, but are not limited to, tissue plasminogen activator (t-PA), interferon, interleukin, growth hormone, histocompatibility and viral envelope glycoprotein signal segments. Suitable fusion segments encoded by fusion segment nucleic acids are disclosed herein. In addition, a

nucleic acid molecule of the present invention can be joined to a fusion segment that directs the encoded protein to the proteosome, such as a ubiquitin fusion segment. Eukaryotic recombinant molecules may also include intervening and/or untranslated sequences surrounding and/or within the nucleic acid sequences of nucleic acid molecules of the present invention.

Another embodiment of the present invention includes a recombinant cell comprising a host cell transformed with one or more recombinant molecules of the present invention. Transformation of a nucleic acid molecule into a cell can be accomplished by any method by which a nucleic acid molecule can be inserted into the cell. Transformation techniques include, but are not limited to, transfection, electroporation, microinjection, lipofection, adsorption, and protoplast fusion. A recombinant cell may remain unicellular or may grow into a tissue, organ or a multicellular organism. Transformed nucleic acid molecules of the present invention can remain extrachromosomal or can integrate into one or more sites within a chromosome of the transformed (i.e., recombinant) cell in such a manner that their ability to be expressed is retained. Preferred nucleic acid molecules with which to transform a cell include TCR V β nucleic acid molecules disclosed herein. Particularly

preferred nucleic acid molecules with which to transform a cell include nCaV β 3₃₈₁, nCaV β 3₃₃₃, nCaV β 3₃₃₀, nCaV β 4₄₀₈, nCaV β 4₃₈₄, nCaV β 4₃₅₁, nCaV β 4₃₃₉, nCaV β 12₄₀₈, nCaV β 12₄₀₂, nCaV β 12₃₃₉, nCaV β 12₃₄₅, nCaV β 72₄₃₈, nCaV β 72₃₉₉, nCaV β 72₄₂₃, nCaV β 72₃₄₂, nCaV β 21₄₆₂, nCaV β 21₃₉₀, nCaV β 21₃₉₆, nCaV β 21₃₄₈, nCaV β 54₄₁₇, nCaV β 54₄₀₅, nCaV β 54₃₅₄, nCaV β 54₃₄₈, nCaV β 182₄₂₃, nCaV β 182₃₈₄, nCaV β 182₃₆₉ and/or nCaV β 182₃₂₇.

Suitable host cells to transform include any cell that can be transformed with a nucleic acid molecule of the present invention. Host cells can be either untransformed cells or cells that are already transformed with at least one nucleic acid molecule (e.g., nucleic acid molecules encoding one or more proteins of the present invention and/or other proteins useful in the production of multivalent vaccines). Host cells of the present invention either can be endogenously (i.e., naturally) capable of producing TCR V β proteins of the present invention or can be capable of producing such proteins after being transformed with at least one nucleic acid molecule of the present invention. Host cells

of the present invention can be any cell capable of producing at least one protein of the present invention, and include bacterial, fungal (including yeast), parasite (including helminth, protozoa and ectoparasite), other insect, other animal and plant cells.

Preferred host cells include bacterial, mycobacterial, yeast, helminth, insect and

5 mammalian cells. More preferred host cells include *Salmonella*, *Escherichia*, *Bacillus*, *Listeria*, *Pichia*, *Saccharomyces*, *Spodoptera*, *Mycobacteria*, *Trichoplusia*, BHK (baby hamster kidney) cells, MDCK cells (Madin-Darby canine kidney cell line), CRFK cells (Crandell feline kidney cell line), CV-1 cells (African monkey kidney cell line used, for example, to culture raccoon poxvirus), COS (e.g., COS-7) cells, chinese hamster ovary
10 (CHO) cells, Ltk cells and Vero cells. Particularly preferred host cells are *Escherichia coli*, including *E. coli* K-12 derivatives; *Salmonella typhi*; *Salmonella typhimurium*, including attenuated strains such as UK-1₀₃₉₈₇ and SR-11₀₄₀₇₂; *Spodoptera frugiperda*; *Trichoplusia ni*; BHK cells; MDCK cells; CRFK cells; CV-1 cells; COS cells; Vero cells; and non-tumorigenic mouse myoblast G8 cells (e.g., ATCC CRL
15 1246). Additional appropriate mammalian cell hosts include other kidney cell lines, other fibroblast cell lines (e.g., human, murine or chicken embryo fibroblast cell lines), myeloma cell lines, Chinese hamster ovary cells, mouse NIH/3T3 cells, LMTK³¹ cells and/or HeLa cells. In one embodiment, the proteins may be expressed as heterologous proteins in myeloma cell lines employing immunoglobulin promoters.

20 A recombinant cell is preferably produced by transforming a host cell with one or more recombinant molecules, each comprising one or more nucleic acid molecules of the present invention operatively linked to an expression vector containing one or more transcription control sequences, examples of which are disclosed herein.

A recombinant cell of the present invention includes any cell transformed with
25 at least one of any nucleic acid molecule of the present invention. Suitable and preferred nucleic acid molecules as well as suitable and preferred recombinant molecules with which to transfer cells are disclosed herein.

It is to be noted that the term "a recombinant molecule", "a host cell" or "a recombinant cell" refers to one or more or at least one recombinant molecule, host cell
30 or recombinant cell, respectively.

Recombinant cells of the present invention can also be co-transformed with one or more recombinant molecules including TCR V β nucleic acid molecules encoding one or more proteins of the present invention and one or more other nucleic acid molecules encoding other therapeutic compounds, as disclosed herein (e.g., to produce multivalent
5 vaccines).

Recombinant DNA technologies can be used to improve expression of transformed nucleic acid molecules by manipulating, for example, the number of copies of the nucleic acid molecules within a host cell, the efficiency with which those nucleic acid molecules are transcribed, the efficiency with which the resultant transcripts are
10 translated, and the efficiency of post-translational modifications. Recombinant techniques useful for increasing the expression of nucleic acid molecules of the present invention include, but are not limited to, operatively linking nucleic acid molecules to high-copy number plasmids, integration of the nucleic acid molecules into one or more host cell chromosomes, addition of vector stability sequences to plasmids, substitutions
15 or modifications of transcription control signals (e.g., promoters, operators, enhancers), substitutions or modifications of translational control signals (e.g., ribosome binding sites, Shine-Dalgarno sequences), modification of nucleic acid molecules of the present invention to correspond to the codon usage of the host cell, deletion of sequences that destabilize transcripts, and use of control signals that temporally separate recombinant
20 cell growth from recombinant enzyme production during fermentation. The activity of an expressed recombinant protein of the present invention may be improved by fragmenting, modifying, or derivatizing nucleic acid molecules encoding such a protein.

Isolated TCR V β proteins of the present invention can be produced in a variety of ways, including production and recovery of natural proteins, production and recovery
25 of recombinant proteins, and chemical synthesis of the proteins. In one embodiment, an isolated protein of the present invention is produced by culturing a cell capable of expressing the protein under conditions effective to produce the protein, and recovering the protein. A preferred cell to culture is a recombinant cell of the present invention. Effective culture conditions include, but are not limited to, effective media, bioreactor,
30 temperature, pH and oxygen conditions that permit protein production. An effective, medium refers to any medium in which a cell is cultured to produce a TCR V β protein

of the present invention. Such medium typically comprises an aqueous medium having assimilable carbon, nitrogen and phosphate sources, and appropriate salts, minerals, metals and other nutrients, such as vitamins. Cells of the present invention can be cultured in conventional fermentation bioreactors, shake flasks, test tubes, microtiter
5 dishes, and petri plates. Culturing can be carried out at a temperature, pH and oxygen content appropriate for a recombinant cell. Such culturing conditions are within the expertise of one of ordinary skill in the art.

Depending on the vector and host system used for production, resultant proteins of the present invention may either remain within the recombinant cell; be secreted into
10 the fermentation medium; be secreted into a space between two cellular membranes, such as the periplasmic space in *E. coli*; or be retained on the outer surface of a cell or viral membrane.

The phrase "recovering the protein", as well as similar phrases, refers to collecting the whole fermentation medium containing the protein and need not imply
15 additional steps of separation or purification. Proteins of the present invention can be purified using a variety of standard protein purification techniques, such as, but not limited to, affinity chromatography, ion exchange chromatography, filtration, electrophoresis, hydrophobic interaction chromatography, gel filtration chromatography,
reverse phase chromatography, concanavalin A chromatography, chromatofocusing and
20 differential solubilization. Proteins of the present invention are preferably retrieved in "substantially pure" form. As used herein, "substantially pure" refers to a purity that allows for the effective use of the protein as a therapeutic composition or diagnostic. A therapeutic composition for animals, for example, should exhibit no substantial toxicity and preferably should be capable of stimulating the production of antibodies in a treated
25 animal.

The present invention also includes isolated (i.e., removed from their natural milieu) antibodies that selectively bind to a TCR V β protein of the present invention or a mimotope thereof (e.g., anti-TCR V β antibodies). As used herein, the term "selectively binds to" a TCR V β protein refers to the ability of antibodies of the present invention to
30 preferentially bind to specified proteins and mimitopes thereof of the present invention. Binding can be measured using a variety of methods standard in the art including

enzyme immunoassays (e.g., ELISA), immunoblot assays, etc.; see, for example, Sambrook et al., *ibid.*, and Harlow, et al., 1988, *Antibodies, a Laboratory Manual*, Cold Spring Harbor Labs Press; Harlow et al., *ibid.* An anti- TCR V β antibody of the present invention preferably selectively binds to a TCR V β protein in such a way as to inhibit
5 the function of that protein.

Isolated antibodies of the present invention can include antibodies in serum, or antibodies that have been purified to varying degrees. Antibodies of the present invention can be polyclonal or monoclonal, or can be functional equivalents such as antibody fragments and genetically-engineered antibodies, including single chain
10 antibodies or chimeric antibodies that can bind to one or more epitopes.

A preferred method to produce antibodies of the present invention includes (a) administering to an animal an effective amount of a protein, peptide or mimetope thereof of the present invention to produce the antibodies and (b) recovering the antibodies. In another method, antibodies of the present invention are produced recombinantly using
15 techniques as heretofore disclosed to produce TCR V β proteins of the present invention. Antibodies raised against defined proteins or mimetopes can be advantageous because such antibodies are not substantially contaminated with antibodies against other
substances that might otherwise cause interference in a diagnostic assay or side effects if used in a therapeutic composition.

20 Antibodies of the present invention have a variety of potential uses that are within the scope of the present invention. For example, such antibodies can be used (a) as reagents in assays to detect TCR V β protein, (b) as reagents in assays to modulate cellular activity through a TCR V β protein (e.g., mimicking ligand binding to TCR V β protein), and/or (c) as tools to screen expression libraries and/or to recover desired
25 proteins of the present invention from a mixture of proteins and other contaminants. Furthermore, antibodies of the present invention can be used to target compounds (e.g., nucleic acid molecules, drugs or proteins) to antigen presenting cells. Targeting can be accomplished by conjugating (i.e., stably joining) such antibodies to the compounds using techniques known to those skilled in the art. Suitable compounds are known to
30 those skilled in the art.

One embodiment of the present invention is a therapeutic composition that, when administered to an animal in an effective manner, is capable of regulating an immune response in an animal. Therapeutic compositions of the present invention include at least one of the following therapeutic compounds: an isolated TCR V β protein of the present invention or a mimetope thereof, an isolated TCR V β nucleic acid molecule of the present invention, an isolated antibody that selectively binds to a TCR V β protein of the present invention, an inhibitor of TCR V β function identified by its ability to bind to a TCR V β protein of the present invention and inhibit binding of a TCR V β protein to MHC, and a mixture thereof (i.e., combination of at least two of the compounds). As used herein, a therapeutic compound refers to a compound that, when administered to an animal in an effective manner, is able to treat, ameliorate, and/or prevent a disease. Examples of proteins, nucleic acid molecules, antibodies and inhibitors of the present invention are disclosed herein.

The present invention also includes a therapeutic composition comprising at least one TCR V β -based compound of the present invention in combination with at least one additional therapeutic compound. Examples of such compounds are disclosed herein.

Therapeutic compositions of the present invention can be administered to any animal susceptible to such therapy, preferably to mammals, and more preferably to dogs.

A therapeutic composition of the present invention is administered to an animal in an effective manner such that the composition is capable of regulating an immune response in that animal. Therapeutic compositions of the present invention can be administered to animals prior to onset of a disease (i.e., as a preventative vaccine) and/or can be administered to animals after onset of a disease in order to treat the disease (i.e., as a therapeutic vaccine). Preferred diseases to prevent or treat include autoimmune diseases, allergic reactions, infectious diseases and cancer.

Therapeutic compositions of the present invention can be formulated in an excipient that the animal to be treated can tolerate. Examples of such excipients include water, saline, Ringer's solution, dextrose solution, Hank's solution, and other aqueous physiologically balanced salt solutions. Nonaqueous vehicles, such as fixed oils, sesame oil, ethyl oleate, or triglycerides may also be used. Other useful formulations include

suspensions containing viscosity enhancing agents, such as sodium carboxymethylcellulose, sorbitol, or dextran. Excipients can also contain minor amounts of additives, such as substances that enhance isotonicity and chemical stability.

Examples of buffers include phosphate buffer, bicarbonate buffer and Tris buffer, while
5 examples of preservatives include thimerosal, o-cresol, formalin and benzyl alcohol. Standard formulations can either be liquid injectables or solids which can be taken up in a suitable liquid as a suspension or solution for injection. Thus, in a non-liquid formulation, the excipient can comprise dextrose, human serum albumin, preservatives, etc., to which sterile water or saline can be added prior to administration.

10 In one embodiment of the present invention, a therapeutic composition can include an adjuvant. Adjuvants are agents that are capable of enhancing the immune response of an animal to a specific antigen. Suitable adjuvants include, but are not limited to, cytokines, chemokines, and compounds that induce the production of cytokines and chemokines (e.g., Flt-3 ligand, granulocyte macrophage colony
15 stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor (M-CSF), colony stimulating factor (CSF), erythropoietin (EPO), interleukin 2 (IL-2), interleukin-3 (IL-3), interleukin 4 (IL-4), interleukin 5 (IL-5), interleukin 6 (IL-6), interleukin 7 (IL-7), interleukin 8 (IL-8), interleukin 10 (IL-10), interleukin 12 (IL-12), interferon gamma, interferon gamma
20 inducing factor I (IGIF), transforming growth factor beta, RANTES (regulated upon activation, normal T cell expressed and presumably secreted), macrophage inflammatory proteins (e.g., MIP-1 alpha and MIP-1 beta), and Leishmania elongation initiating factor (LEIF)); bacterial components (e.g., endotoxins, in particular superantigens, exotoxins and cell wall components); aluminum-based salts; calcium-based salts; silica;
25 polynucleotides; toxoids; serum proteins, viral coat proteins; block copolymer adjuvants (e.g., Hunter's Titermax™ adjuvant (Vaxcel™, Inc. Norcross, GA), Ribi adjuvants (Ribi ImmunoChem Research, Inc., Hamilton, MT); and saponins and their derivatives (e.g., Quil A (Superfos Biosector A/S, Denmark). Protein adjuvants of the present invention can be delivered in the form of the protein themselves or of nucleic acid molecules
30 encoding such proteins using the methods described herein. A therapeutic composition can contain one or more adjuvants.

In one embodiment of the present invention, a therapeutic composition can include a carrier. Carriers include compounds that increase the half-life of a therapeutic composition in the treated animal. Suitable carriers include, but are not limited to, polymeric controlled release vehicles, biodegradable implants, liposomes, bacteria, 5 viruses, other cells, oils, esters, and glycols. A therapeutic composition can contain one or more carriers.

One embodiment of the present invention is a controlled release formulation that is capable of slowly releasing a composition of the present invention into an animal. As used herein, a controlled release formulation comprises a composition of the present 10 invention in a controlled release vehicle. Suitable controlled release vehicles include, but are not limited to, biocompatible polymers, other polymeric matrices, capsules, microcapsules, microparticles, bolus preparations, osmotic pumps, diffusion devices, liposomes, lipospheres, and transdermal delivery systems. Other controlled release formulations of the present invention include liquids that, upon administration to an 15 animal, form a solid or a gel *in situ*. Preferred controlled release formulations are biodegradable (i.e., bioerodible).

A preferred controlled release formulation of the present invention is capable of releasing a composition of the present invention into the blood of the treated animal at a constant rate sufficient to attain therapeutic dose levels of the composition to regulate an 20 immune response in an animal. The therapeutic composition is preferably released over a period of time ranging from about 1 to about 12 months. A controlled release formulation of the present invention is capable of effecting a treatment preferably for at least about 1 month, more preferably for at least about 3 months, even more preferably for at least about 6 months, even more preferably for at least about 9 months, and even 25 more preferably for at least about 12 months.

Therapeutic compositions of the present invention can be administered to animals prior to and/or after onset of disease. Acceptable protocols to administer therapeutic compositions in an effective manner include individual dose size, number of doses, frequency of dose administration, and mode of administration. Determination of 30 such protocols can be accomplished by those skilled in the art. A suitable single dose is a dose that is capable of regulating the immune response in an animal when administered

-51-

one or more times over a suitable time period. For example, a preferred single dose of a protein, mimetope or antibody therapeutic composition is from about 1 microgram (g) to about 10 milligrams (mg) of the therapeutic composition per kilogram body weight of the animal. Booster vaccinations can be administered from about 2 weeks to several
5 years after the original administration. Booster administrations preferably are administered when the immune response of the animal becomes insufficient to protect the animal from disease. A preferred administration schedule is one in which from about 10 g to about 1 mg of the therapeutic composition per kg body weight of the animal is administered from about one to about two times over a time period of from
10 about 2 weeks to about 12 months. Modes of administration can include, but are not limited to, subcutaneous, intradermal, intravenous, intranasal, intraocular, oral, transdermal and intramuscular routes.

According to one embodiment, a nucleic acid molecule of the present invention can be administered to an animal in a fashion to enable expression of that nucleic acid
15 molecule into a therapeutic protein or therapeutic RNA (e.g., antisense RNA, ribozyme, triple helix forms or RNA drug) in the animal. Nucleic acid molecules can be delivered to an animal in a variety of methods including, but not limited to, (a) administering a naked (i.e., not packaged in a viral coat or cellular membrane) nucleic acid as a genetic vaccine (e.g., as naked DNA or RNA molecules, such as is taught, for example in Wolff
20 et al., 1990, *Science* 247, 1465-1468) or (b) administering a nucleic acid molecule packaged as a recombinant virus vaccine or as a recombinant cell vaccine (i.e., the nucleic acid molecule is delivered by a viral or cellular vehicle). One or more nucleic acid molecules can be delivered to an animal.

A genetic (i.e., naked nucleic acid) vaccine of the present invention includes a
25 nucleic acid molecule of the present invention and preferably includes a recombinant molecule of the present invention that preferably is replication, or otherwise amplification, competent. A genetic vaccine of the present invention can comprise one or more nucleic acid molecules of the present invention in the form of, for example, a dicistronic recombinant molecule. Preferred genetic vaccines include at least a portion
30 of a viral genome (i.e., a viral vector). Preferred viral vectors include those based on alphaviruses, poxviruses, adenoviruses, herpesviruses, picornaviruses, and retroviruses,

-52-

with those based on alphaviruses (such as sindbis or Semliki forest virus), species-specific herpesviruses and poxviruses being particularly preferred. Any suitable transcription control sequence can be used, including those disclosed as suitable for protein production. Particularly preferred transcription control sequences include

5 cytomegalovirus immediate early (preferably in conjunction with Intron-A), Rous sarcoma virus long terminal repeat, and tissue-specific transcription control sequences, as well as transcription control sequences endogenous to viral vectors if viral vectors are used. The incorporation of a "strong" polyadenylation signal is also preferred.

Genetic vaccines of the present invention can be administered in a variety of

10 ways, with intramuscular, subcutaneous, intradermal, transdermal, intranasal and oral routes of administration being preferred. A preferred single dose of a genetic vaccine ranges from about 1 nanogram (ng) to about 600 g, depending on the route of administration and/or method of delivery, as can be determined by those skilled in the art. Suitable delivery methods include, for example, by injection, as drops, aerosolized

15 and/or topically. Genetic vaccines of the present invention can be contained in an aqueous excipient (e.g., phosphate buffered saline) alone or in a carrier (e.g., lipid-based vehicles).

A recombinant virus vaccine of the present invention includes a recombinant molecule of the present invention that is packaged in a viral coat and that can be

20 expressed in an animal after administration. Preferably, the recombinant molecule is packaging- or replication-deficient and/or encodes an attenuated virus. A number of recombinant viruses can be used, including, but not limited to, those based on alphaviruses, poxviruses, adenoviruses, herpesviruses, picornaviruses, and retroviruses. Preferred recombinant virus vaccines are those based on alphaviruses (such as Sindbis

25 virus), raccoon poxviruses, species-specific herpesviruses and species-specific poxviruses. An example of methods to produce and use alphavirus recombinant virus vaccines are disclosed in PCT Publication No. WO 94/17813, by Xiong et al., published August 18, 1994.

When administered to an animal, a recombinant virus vaccine of the present

30 invention infects cells within the immunized animal and directs the production of a therapeutic protein or RNA nucleic acid molecule that is capable of protecting the

-53-

animal from disease caused by a parasitic helminth as disclosed herein. For example, a recombinant virus vaccine comprising a TCR V β nucleic acid molecule of the present invention is administered according to a protocol that results in the regulation of an immune response in an animal. A preferred single dose of a recombinant virus vaccine of the present invention is from about 1×10^4 to about 1×10^8 virus plaque forming units (pfu) per kilogram body weight of the animal. Administration protocols are similar to those described herein for protein-based vaccines, with subcutaneous, intramuscular, intranasal, intraocular and oral administration routes being preferred. One or more recombinant virus vaccines can be delivered to an animal.

10 A recombinant cell vaccine of the present invention includes recombinant cells of the present invention that express at least one protein of the present invention. Preferred recombinant cells for this embodiment include *Salmonella*, *E. coli*, *Listeria*, *Mycobacterium*, *S. frugiperda*, yeast, (including *Saccharomyces cerevisiae* and *Pichia pastoris*), BHK, CV-1, myoblast G8, COS (e.g., COS-7), Vero, MDCK and CRFK
15 recombinant cells. Recombinant cell vaccines of the present invention can be administered in a variety of ways but have the advantage that they can be administered orally, preferably at doses ranging from about 10^8 to about 10^{12} cells per kilogram body weight. Administration protocols are similar to those described herein for protein-based vaccines. Recombinant cell vaccines can comprise whole cells, cells stripped of cell
20 walls or cell lysates.

The efficacy of a therapeutic composition of the present invention to regulate the immune response in an animal can be tested in a variety of ways including, but not limited to, detection of cellular immunity within the treated animal, determination of T cell activity (helper or cytotoxic T cell activity), identification of T cell repertoire,
25 detection of immunoregulatory cytokines, e.g., IL-2, IL-4, IL-10, IL-12, levels, detection of antibody levels, determine tumor development or challenge of the treated animal with an infectious agent to determine whether the treated animal is resistant to disease. In one embodiment, therapeutic compositions can be tested in animal models such as mice. Such techniques are known to those skilled in the art.

30 According to the present invention, a therapeutic composition is used to treat a disease requiring immunological regulation, such as cancer, infectious diseases,

autoimmune diseases or allergy. Suitable cancers to treat include lymphomas or leukemias. Suitable infectious diseases to treat include diseases caused by viral, bacterial, yeast, fungal or parasitic infection. Suitable autoimmune diseases to treat include: autoimmune skin diseases, e.g. pemphigus foliaceus, pemphigus vulgaris, pemphigus vegetans, pemphigus erythematosis, bullous pemphigoid, discoid lupus, dermatomyositis or subcorneal pustular dermatosis; blood disorders, e.g. autoimmune hemolytic anemia, immune-mediated thrombocytopenia, aplastic anemia, pure red cell aplasia or immune mediated neutropenia; endocrine dysfunction, e.g. lymphocytic thyroiditis, diabetes, hypoadrenocorticism or hypoparathyroidism; multi-system dysfunction, e.g. systemic lupus erythematosus or Sjogren's syndrome; neurologic dysfunction, e.g. myasthenia gravis, distemper and rabies post vaccinal encephalopathy or acute polyradiculoneuritis; or musculoskeletal disease, e.g. rheumatoid arthritis, idiopathic polyarthritis, plasmacytic-lymphocytic arthritis or polymyositis. Suitable allergies to treat include allergic dermatitis, atopic dermatitis, allergic rhinitis or allergic bronchitis.

One therapeutic composition of the present invention includes a TCR V β protein of the present invention, or a portion of such TCR V β protein that elicits a cytotoxic T cell response against a T cell bearing the TCR V β protein. A preferred TCR V β protein comprises a soluble form of a TCR V β protein of the present invention, with a peptide of a TCR V β protein being more preferred. A preferred TCR V β peptide is from about 5 to about 50 residues, more preferably from about 10 to about 40 residues and even more preferably from about 12 to about 30 residue in length. One or more TCR V β proteins of the present invention, or portions of such TCR V β proteins can be used in a therapeutic composition.

According to the present invention, a therapeutic composition comprising a TCR V β peptide, e.g. a portion of a polypeptide, can be delivered to an animal as a peptide or in the form of DNA encoding such peptide. A TCR V β peptide of the present invention can be linked to another molecule to assist in the delivery of the peptide to an animal. Preferably, a TCR V β peptide of the present invention is administered systemically to an animal. One or more peptides can be used in a therapeutic composition.

Another therapeutic composition of the present invention includes an inhibitory compound that inhibits a TCR V β protein from binding to MHC. An inhibitory compound is capable of substantially interfering with the function of a TCR V β protein susceptible to inhibition. For example, an inhibitory compound is administered in an amount and manner that inhibits an immune response that is sufficient to treat an animal for a disease that requires downregulation of an immune response. One or more inhibitors can be used in a therapeutic composition.

Suitable inhibitory compounds include compounds that prevent the activation of an immunoregulatory cell through TCR V β by, for example, interfering with the binding of TCR V β protein to MHC by binding to either the TCR V β protein or MHC. An example of an inhibitory compound is an antibody of the present invention, administered to an animal in an effective manner; i.e., an antibody of the present invention, is administered in an amount so as to be present in the animal at a titer that is sufficient, upon interaction of that antibody with a native TCR V β protein, to decrease TCR V β activity in an animal, at least temporarily. Oligonucleotide nucleic acid molecules of the present invention can also be administered in an effective manner, thereby reducing expression of TCR V β proteins in order to interfere with TCR V β activity targeted in accordance with the present invention. Peptides of TCR V β proteins of the present invention can also be administered in an effective manner, thereby reducing binding of TCR V β proteins to MHC in order to interfere with TCR V β activity targeted in accordance with the present invention. Preferably, an inhibitory compound is derived from a TCR V β protein of the present invention.

An inhibitory compound of TCR V β function can be identified using TCR V β proteins of the present invention. One embodiment of the present invention is a method to identify a compound capable of inhibiting TCR V β function. Such a method includes the steps of: (a) contacting (e.g., combining, mixing) an isolated TCR V β protein of the present invention, with a putative inhibitory compound under conditions in which, in the absence of the compound, the protein binds to a protein including MHC, and (b) determining if the putative inhibitory compound inhibits the binding of TCR V β to MHC. Putative inhibitory compounds to screen include small organic molecules, antibodies (including mimetopes thereof), and ligand analogs. Such compounds can

-56-

also be screened to identify those compounds that are substantially not toxic to a recipient animal.

One embodiment of the present invention is a method to detect expansion of T cells in an animal. The present method utilizes the discovery by the inventors of unique sequences in a TCR V β and more particularly in the V region of a TCR V β that function, or can be used, as markers for T cells. As used herein, the term "unique sequences" refers to nucleic acid or amino acid sequences that are present in one TCR V β nucleic acid molecule or TCR V β protein, but not in another TCR V β nucleic acid molecule or TCR V β protein, respectively. Thus, a unique sequence differentiates one TCR V β nucleic acid molecule or TCR V β protein of the present invention from another TCR V β nucleic acid molecule or TCR V β protein, respectively. For example, a unique sequence within hcV β 3, is not found within hcV β 4, hcV β 12, hcV β 72, hcV β 21, dtb54 or dtb182, and a unique sequence within hcV β 4, is not found within hcV β 3, hcV β 12, hcV β 72, hcV β 21, dtb54 or dtb182, and so on. A unique sequence of the present invention can be used to detect expansion of T cells by, for example, determining the presence or absence of any one or more unique sequences, determining increased or decreased levels of molecules carrying one or more unique sequences compared with other unique sequences in the same animal and/or a different animal, or comparing levels of different TCR V β proteins in an animal.

It is within the scope of the present invention that any unique sequence present in a TCR V β sequence of the present invention can be used in the practice of the present method, including those identified herein and those which will be identified based on the sequences of nucleic acid molecules or proteins disclosed herein. Preferably, unique sequences of the present invention include those sequences located within about the first 200 nucleotides or about the first 70 residues of the 5' or amino terminus of a nucleic acid molecule or a protein. The suitable length of a unique sequence depends upon the reagent used to detect the presence of the unique sequence. For example, a suitable length of a unique sequence is from about 15 to about 30 nucleotides if the detection reagent is a DNA primer. Alternatively, a suitable length of a unique sequence is from about 50 to about 300 nucleotides if the detection reagent is a DNA hybridization probe. Alternatively, a suitable length of a unique sequence is at least about 5 amino acids if the

-57-

detection reagent is an antibody. In addition, one or more unique sequences can be identified, and one or more reagents can be used to identify such sequences, using a method of the present invention.

Any method of the present invention can be used to determine the presence,
5 absence, amount or ratio of TCR V β 's of the present invention in an animal to determine T cell expansion and/or diagnose an abnormal state or a specific disease. Typically, numbers of T cells in an animal are regulated. Expansion of total T cell numbers, or of a particular T cell clone, can represent an abnormal state or disease. For example, a particular T cell clone is expanded in a T cell lymphoma or leukemia. Thus, information
10 derived using the present methods is particularly useful because the inventors have discovered the seven different TCR V β proteins disclosed herein which can comprise at least about 95% of the TCR V β repertoire in canids. The discovery of the existence of a small repertoire of TCR V β proteins enables the production of appropriate reagents that detect a substantial amount of T cell receptors in an animal. The reagents can be used to
15 correlate T cell expansion with a specific disease by comparing results obtained using samples from normal animals compared with animals having or suspected of having a disease. Thus, any diagnostic method of the present invention is useful for determining
if an animal is susceptible to, has or is in remission from a disease.

According to the present invention, T cell expansion is determined by detecting
20 increased levels of one or more specific TCR V β molecules in a tissue sample isolated from an animal. Increased levels of TCR V β molecules can be determined by comparing levels of two or more different TCR V β molecules in a tissue sample isolated from one animal, or levels of one or more TCR V β molecules in tissue samples from two or more different animals. Total amounts or ratios of particular TCR V β molecules can be
25 determined by one of skill in the art depending upon the method used to detect the presence of a TCR V β molecule in a sample. Preferably, a ratio illustrative of increased levels of a particular TCR V β molecule is from about 2-fold to about 5-fold, more preferably from about 5-fold to about 25, and more preferably 10-fold more of one particular TCR V β molecule compared with another sample of the same TCR V β
30 molecule or a different TCR V β molecule. Methods to determine ratios are known to

-58-

those in the art and include, for example, densitometry, spectrophotometry or determining counts per minute of isotopes.

One embodiment of the present invention is a method to detect expansion of T cells in an animal comprising detecting the presence of one or more T cell receptors having unique nucleic acid sequences within hcV β 3, hcV β 4, hcV β 12, hcV β 72, hcV β 21, dtb54 or dtb182 nucleic acid molecules or hcV β 3, hcV β 4, hcV β 12, hcV β 72, hcV β 21, dtb54 or dtb182 proteins by forming detectable products, wherein the increased level of a detectable product compared with another detectable product indicates expansion of the T cells. According to the present method, a suitable sample containing T cells is isolated from an animal. Samples containing T cell receptors can be isolated from the same or different animals. Control samples can be obtained from the same or different animals. The sample is contacted under appropriate conditions with one or more reagents capable of identifying one or more unique nucleic acid or amino acid sequences, respectively. Preferably, a reagent distinguishes one member of the group comprising hcV β 3, hcV β 4, hcV β 12, hcV β 72, hcV β 21, hcV β 54 or hcV β 182 nucleic acid molecules or hcV β 3, hcV β 4, hcV β 12, hcV β 72, hcV β 21, hcV β 54 or hcV β 182 proteins, preferably nCaV β 3₃₈₁, nCaV β 4₄₀₈, nCaV β 12₄₀₈, nCaV β 72₄₃₈, nCaV β 21₄₆₂, nCaV β 54₄₁₇, nCaV β 182₄₂₃, PCaV β 3₁₂₇, PCaV β 4₁₂₈, PCaV β 12₁₃₄, PCaV β 72₁₃₃, PCaV β 21₁₃₀, PCaV β 54₁₃₅ or PCaV β 182₁₂₈, from another member of that group. By determining increased production of one of the detectable products, one can detect T cell expansion. Preferably, expansion of a T cell is determined by comparing formation of one detectable product with formation of one or more other detectable products and looking for increased production of at least one of the products compared to another. According to the present invention, a detectable product can comprise a nucleic acid molecule, a peptide, a protein or an antibody. Preferred detectable products and methods to form detectable products are disclosed herein. It is within the skill of one in the art that methods to identify detectable products based on the product being detected.

The invention also provides novel reagents useful in the methods which have been described herein above. Thus, the invention includes reagents capable of binding to unique nucleic acid or unique amino acid sequences contained within a TCR V β . Preferred reagents include those which can differentiate one TCR V beta protein, or

nucleic acid molecule, from another. Preferred reagents can distinguish TCR V beta proteins hcV β 2, hcV β 3, hcV β 12, hcV β 72, hcV β 21, dtb54 or dtb182, or the nucleic acid molecules that encode them, from each other. More preferred reagents can distinguish proteins comprising PCaV β 3₁₂₇, PCaV β 3₁₁₁, PCaV β 3₁₁₀, PCaV β 4₁₂₈, PCaV β 4₁₁₃,
5 PCaV β 4₁₀₉, PCaV β 12₁₃₄, PCaV β 12₁₁₁, PCaV β 12₁₁₅, PCaV β 72₁₃₃, PCaV β 72₁₁₃,
PCaV β 72₁₁₄, PCaV β 21₁₃₀, PCaV β 21₁₀₈, PCaV β 21₁₁₆, PCaV β 54₁₃₅, PCaV β 54₁₁₄,
PCaV β 54₁₁₆, PCaV β 182₁₂₈, PCaV β 182₁₁₀ and/or PCaV β 182₁₀₉ from each other, or
nucleic acid molecules comprising nCaV β 3₃₈₁, nCaV β 3₃₃₃, nCaV β 3₃₃₀, nCaV β 4₄₀₈,
nCaV β 4₃₈₄, nCaV β 4₃₅₁, nCaV β 4₃₃₉, nCaV β 12₄₀₈, nCaV β 12₄₀₂, nCaV β 12₃₃₉, nCaV β 12₃₄₅,
10 nCaV β 72₄₃₈, nCaV β 72₃₉₉, nCaV β 72₄₂₃, nCaV β 72₃₄₂, nCaV β 21₄₆₂, nCaV β 21₃₉₀,
nCaV β 21₃₉₆, nCaV β 21₃₄₈, nCaV β 54₄₁₇, nCaV β 54₄₀₅, nCaV β 54₃₅₄, nCaV β 54₃₄₈,
nCaV β 182₄₂₃, nCaV β 182₃₈₄, nCaV β 182₃₆₉ and/or nCaV β 182₃₂₇ from each other. Even
more preferred reagents can distinguish TCR V beta proteins comprising amino acid
sequence SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID
15 NO:41, SEQ ID NO:44, SEQ ID NO:47 from each other.

In particular, a method of the present invention comprises: (a) contacting a sample, i.e., one or more samples, containing DNA from T cells with a reagent, i.e., one or more reagents, having specificity for a unique nucleic acid sequence; and (b) determining the presence of DNA carrying the unique nucleic acid sequences. Methods
20 to determine the presence of the DNA are disclosed herein.

In one embodiment, identifying the presence of a T cell receptor having unique sequence can be achieved by polymerase chain reaction (PCR) amplification techniques known to those of skill in the art. The PCR amplification forms a detectable product comprising DNA. An example of a suitable reagent to use in PCR amplification
25 techniques is a DNA primer complementary to all or a portion of a unique nucleic acid sequence, referred to herein as a unique sequence primer. Preferably, another primer is used in conjunction with the unique sequence primer in order to effect amplification. This second primer can be complementary to a unique sequence or to a common sequence (i.e., a sequence shared by different TCR beta chain sequences). Typically, the
30 second primer is complementary to a common sequence and is chosen based on its distance from the unique sequence primer, i.e. based on ease of detection of PCR

amplification product. One of skill in the art understands that a preferred product of a PCR reaction is from about 100 to about 500 nucleotides, preferably from about 150 to about 450 nucleotides and more preferably from about 200 to about 400 nucleotides. Thus, it is within the skill of one in the art to design and create a second primer located from about 100 to about 500 nucleotides from the site of a unique sequence. For example, a suitable second primer includes a DNA primer complementary to a sequence in the constant region of a beta chain. Preferred second primers are described herein in the Examples section. Methods to resolve PCR products are well known to those of skill in the art. In addition, methods to quantitate the amount of PCR product produced in a PCR reaction are well known to those of skill in the art. Examples of preferred unique nucleic acid sequences to be identified by PCR include unique sequences contained within SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27 and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80. More preferred unique nucleic acid sequences to be identified by PCR include SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55 and/or SEQ ID NO:56, or complements thereof. Preferred second primers include primers located in the constant region sequence of a beta chain. More preferred second primers include SEQ ID NO:58 and SEQ ID NO:59, or complements thereof.

In another embodiment, identifying the presence of a T cell receptor having a unique nucleic acid sequence can be achieved by nucleic acid, e.g., DNA, RNA, modified DNA or modified RNA, hybridization techniques using a nucleic acid probe. The hybridization forms a detectable product comprising a hybrid between the nucleic acid and the reagent. A suitable reagent for use with hybridization techniques include nucleic acid probes which are complementary to nucleic acid sequences that include all

-61-

or a portion of a unique sequence. The hybridization forms a detectable product comprising a hybrid between the nucleic acid and the reagent. It is within the skill of one in the art to design and produce suitable probes based on sequences of the present invention. The presence of a unique sequence in a sample from an animal is determined
5 by detecting the hybridization of a "unique sequence" probe to that unique sequence in the TCR V β nucleic acid molecule. Methods to detect hybridization of a probe are well known to those of skill in the art and include those that allow one to distinguish one V β nucleic acid from another. In addition, methods to quantitate the extent of hybridization are well known to those of skill in the art. Preferred unique nucleic acid sequences to be
10 identified by nucleic acid hybridization include unique sequences contained within SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27 and/or a nucleic acid molecule
15 that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80. More
20 preferred unique nucleic acid sequences to be identified by nucleic acid hybridization include unique sequences SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55 and/or SEQ ID NO:56.

A unique amino acid sequence of the present invention can be used to produce antibodies that bind specifically to the portion of a TCR V β protein that contains the
25 unique amino acid sequence. Such antibodies can be monoclonal or polyclonal, and produced using methods described herein. The antibodies can be used to detect T cells having T cell receptors containing such unique sequences by contacting T cells isolated from an animal with the antibody under appropriate conditions known in the art that enable formation of a complex between an antibody and a T cell receptor in a specific
30 manner, i.e., such that the antibody only binds specifically a particular TCR V β . The complex between an antibody and a T cell receptor is a detectable product. Methods to

- 62 -

detect such complex formation are known to those of skill in the art and include, for example, using a detectable moiety such as a radioisotope, an enzyme or a fluorescent dye, to detect complex formation. Preferred unique amino acid sequences to be identified using antibodies include antibodies that bind specifically to a unique amino acid sequence contained within SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:20, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:41, SEQ ID NO:44, SEQ ID NO:47, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80. Particularly preferred unique amino acid sequences to be identified using antibodies include antibodies that bind specifically to unique amino acid sequences encoded by a nucleic acid sequence SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56.

In another embodiment, identifying the presence of a T cell receptor having a unique nucleic acid sequence can be achieved by PCR amplification and nucleic acid sequencing techniques. Suitable reagents for use with such techniques include DNA primers which are complementary to common sequences (i.e., sequences shared by two or more TCR V β molecules) that flank all or a portion of a unique sequence. It is within the skill of one in the art to design and produce suitable primers based on sequences of the present invention. The presence of a unique sequence in a sample from an animal is determined by sequencing the PCR product produced using the common sequence primers and identifying whether one or more nucleic acid sequences are present in the PCR product. An example of such method is described in Example 4 herein. Methods to produce and sequence PCR products are well known to those of skill in the art. T cell expansion is determined by identifying the heterogeneity or homogeneity of nucleic acid sequence displayed in a DNA fingerprint profile of a given sequence in a given sample of PCR products.

Preferred reagents include, but are not limited to, DNA primers or probes complementary to unique nucleic acid sequences contained in SEQ ID NO:1, SEQ ID

NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27 and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80, including DNA primers or probes comprising SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or complements of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56; or antibodies that bind specifically to an amino acid sequence encoded by a comprising SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55 and/or SEQ ID NO:56, or to other unique amino acid sequences in larger proteins.

One embodiment of the present invention is a method of detecting T cell expansion in an animal comprising detecting the expansion of a T cell receptor having a unique amino acid sequence within a protein selected from the group consisting of hcV β 3, hcV β 4, hcV β 12, hcV β 72, hcV β 21, dtb54 or dtb182 proteins by forming detectable products, wherein the increased level of a detectable product compared with another detectable product indicates expansion of the T cells. Preferred V β proteins containing unique amino acid sequence include PCaV β 3₁₂₇, PCaV β 3₁₁₁, PCaV β 3₁₁₀, PCaV β 4₁₂₈, PCaV β 4₁₁₃, PCaV β 4₁₀₉, PCaV β 12₁₃₄, PCaV β 12₁₁₁, PCaV β 12₁₁₅, PCaV β 72₁₃₃, PCaV β 72₁₁₃, PCaV β 72₁₁₄, PCaV β 21₁₃₀, PCaV β 21₁₀₈, PCaV β 21₁₁₆, PCaV β 54₁₃₅, PCaV β 54₁₁₄, PCaV β 54₁₁₆, PCaV β 182₁₂₈, PCaV β 182₁₁₀ and/or PCaV β 182₁₀₉.

Examples of samples useful a method of the present invention include samples from an animal that contains T cells. Preferably, a sample to be tested using a method of the present invention comprises blood, synovial fluid, lung lavage, saliva, spleen, thymus, tumors, granulomas, abscesses, edematous fluid, central nervous system fluid.

- 64 -

Preferred animals from which to isolate a sample of the present invention includes a mammal, more preferably a canid and more preferably a dog.

Any method of the present invention can be used to determine the disease state of an animal. Such methods can be used to determine the presence or absence of disease in an animal, including an animal susceptible to disease, an animal suspected of having disease, an animal having disease or an animal being or having been treated for a disease. Examples of specific diseases that can be diagnosed using a method of the present invention include: various forms of cancer, e.g., lymphoma and leukemia; various autoimmune diseases, e.g., rheumatoid arthritis or diabetes; various infectious diseases, such as those caused by viruses, by a yeast, e.g. of the genus *Candida*, by a parasite, e.g., *Trichinella*, *Leishmania*, *Toxoplasma*, a filariid, a mycobacterium, a protozoan, and by a bacterium; and allergies involving T cells, e.g. allergic dermatitis, atopic dermatitis, allergic bronchitis or allergic rhinitis.

A preferred embodiment of the present invention is a method to diagnose T cell cancer comprising: (a) contacting a sample containing DNA from an animal with a DNA primer that is complementary to a unique nucleic acid sequence within a nucleic acid molecule including nCaV β 3₃₈₁, nCaV β 3₃₃₃, nCaV β 3₃₃₀, nCaV β 4₄₀₈, nCaV β 4₃₈₄, nCaV β 4₃₅₁, nCaV β 4₃₃₉, nCaV β 12₄₀₈, nCaV β 12₄₀₂, nCaV β 12₃₃₉, nCaV β 12₃₄₅, nCaV β 72₄₃₈, nCaV β 72₃₉₉, nCaV β 72₄₂₃, nCaV β 72₃₄₂, nCaV β 21₄₆₂, nCaV β 21₃₉₀, nCaV β 21₃₉₆, nCaV β 21₃₄₈, nCaV β 54₄₁₇, nCaV β 54₄₀₅, nCaV β 54₃₅₄, nCaV β 54₃₄₈, nCaV β 182₄₂₃, nCaV β 182₃₈₄, nCaV β 182₃₆₉ or nCaV β 182₃₂₇; and (b) diagnosing the cancer by determining the amount of DNA containing the unique nucleic acid sequence by comparing the amount so determined with the amount of DNA containing the unique sequence from a normal animal. According to the present invention, "a DNA primer" refers to one or more primers and "a unique nucleic acid sequence" refers to one or more unique nucleic acid sequences.

Another preferred embodiment of the present invention is a method to diagnose T cell cancer comprising: (a) contacting a sample containing DNA from an animal with a DNA primer that is complementary to a unique nucleic acid sequence within nucleic acid molecule selected from the group consisting of nCaV β 3₃₈₁, nCaV β 3₃₃₃, nCaV β 3₃₃₀, nCaV β 4₄₀₈, nCaV β 4₃₈₄, nCaV β 4₃₅₁, nCaV β 4₃₃₉, nCaV β 12₄₀₈, nCaV β 12₄₀₂, nCaV β 12₃₃₉,

nCaV β 12₃₄₅, nCaV β 72₄₃₈, nCaV β 72₃₉₉, nCaV β 72₄₂₃, nCaV β 72₃₄₂, nCaV β 21₄₆₂,
 nCaV β 21₃₉₀, nCaV β 21₃₉₆, nCaV β 21₃₄₈, nCaV β 54₄₁₇, nCaV β 54₄₀₅, nCaV β 54₃₅₄,
 nCaV β 54₃₄₈, nCaV β 182₄₂₃, nCaV β 182₃₈₄, nCaV β 182₃₆₉ or nCaV β 182₃₂₇; and (b)
 diagnosing cancer by quantitatively determining the ratio of DNA containing each of the
 5 unique nucleic acid sequences and by comparing the amount of DNA containing each of
 the unique sequence with each other.

The present invention also includes a kit comprising one or more reagents of the
 present invention. Preferred reagents include those which can differentiate TCR V beta
 proteins or nucleic acid molecules that encode such proteins. Preferred TCR V beta
 10 proteins include hcV β 2, hcV β 3, hcV β 12, hcV β 72, hcV β 21, dtb54 or dtb182, with
 PCaV β 3₁₂₇, PCaV β 3₁₁₁, PCaV β 3₁₁₀, PCaV β 4₁₂₈, PCaV β 4₁₁₃, PCaV β 4₁₀₉, PCaV β 12₁₃₄,
 PCaV β 12₁₁₁, PCaV β 12₁₁₅, PCaV β 72₁₃₃, PCaV β 72₁₁₃, PCaV β 72₁₁₄, PCaV β 21₁₃₀,
 PCaV β 21₁₀₈, PCaV β 21₁₁₆, PCaV β 54₁₃₅, PCaV β 54₁₁₄, PCaV β 54₁₁₆, PCaV β 182₁₂₈,
 PCaV β 182₁₁₀ and/or PCaV β 182₁₀₉ being more preferred and proteins comprising SEQ ID
 15 NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:20, SEQ ID NO:23,
 SEQ ID NO:26, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ
 ID NO:41, SEQ ID NO:44, SEQ ID NO:47, SEQ ID NO:60, SEQ ID NO:61, SEQ ID
 NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID
 NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID
 20 NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID
 NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80 and/or proteins encoded by the
 complement of a nucleic acid sequence including SEQ ID NO:50, SEQ ID NO:51, SEQ
 ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56 being even
 more preferred. Preferred TCR V beta nucleic acid molecules include hcV β 2, hcV β 3,
 25 hcV β 12, hcV β 72, hcV β 21, dtb54 or dtb182, with nCaV β 3₃₈₁, nCaV β 3₃₃₃, nCaV β 3₃₃₀,
 nCaV β 4₄₀₈, nCaV β 4₃₈₄, nCaV β 4₃₅₁, nCaV β 4₃₃₉, nCaV β 12₄₀₈, nCaV β 12₄₀₂, nCaV β 12₃₃₉,
 nCaV β 12₃₄₅, nCaV β 72₄₃₈, nCaV β 72₃₉₉, nCaV β 72₄₂₃, nCaV β 72₃₄₂, nCaV β 21₄₆₂,
 nCaV β 21₃₉₀, nCaV β 21₃₉₆, nCaV β 21₃₄₈, nCaV β 54₄₁₇, nCaV β 54₄₀₅, nCaV β 54₃₅₄,
 nCaV β 54₃₄₈, nCaV β 182₄₂₃, nCaV β 182₃₈₄, nCaV β 182₃₆₉ and/or nCaV β 182₃₂₇ being more
 30 preferred and nucleic acid molecules comprising sequences SEQ ID NO:1, SEQ ID
 NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ

-66-

ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, a complement of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80, and complements thereof, being even more preferred. A kit of the present invention can include mixtures of reagents disclosed herein.

The following examples are provided for the purposes of illustration and are not intended to limit the scope of the present invention.

EXAMPLES

It is to be noted that the examples include a number of molecular biology, microbiology, immunology and biochemistry techniques considered to be familiar to those skilled in the art. Disclosure of such techniques can be found, for example, in Sambrook et al., *ibid.* and Ausubel, et al., 1993, *Current Protocols in Molecular Biology*, Greene/Wiley Interscience, New York, NY, and related references. It should also be noted that since nucleic acid sequencing technology, and in particular the sequencing of PCR products, is not entirely error-free, that the nucleic acid and deduced protein sequences presented herein represent apparent nucleic acid sequences of the nucleic acid molecules encoding TCR V β proteins of the present invention.

Example 1

This example describes the isolation and sequencing of canine T cell receptor (TCR) V β nucleic acid molecules.

Canine TCR V β nucleic acid molecules were produced as follows. RNA was purified from mitogen activated canine peripheral blood lymphocytes and resuspended in water at about 2.5×10^5 cell equivalent/microliter (μ l). About 5 μ l of RNA and random hexanucleotide primers were used to synthesize cDNA using the First Strand cDNA Synthesis™ kit (available from Pharmacia, Uppsala, Sweden). TCR V β genes were selectively PCR amplified from the cDNA using degenerate oligonucleotides designed using the conserved sequence motifs WYRQ and Y(Y/F)CA of T and B cell antigen receptors (Rast and Litman, *Proc. Natl. Acad. Sci. USA*, vol. 91, p. 9248, 1994). The degenerate primer FR2, having the nucleic acid sequence 5' CCG AAT TCT GGT A(TC) C(GA) NCA 3' (SEQ ID NO:81) was used in combination with either the FR3A primer, having the nucleic acid sequence 5' CGG ATC CGC (GA)CA (GA)TA (GA)T A 3' (SEQ ID NO:82) or the primer FR3B, having the nucleic acid sequence 5' CGG ATC CGC (GA)CA (GA)A A(GA)T A 3' (SEQ ID NO:83). First round PCR reactions were performed in about 50 μ l of 50 mM KCl, 10 mM Tris-HCl, 0.01% gelatin (pH 8.3), 3.5 mM MgCl₂, 0.2 mM of each of the four deoxyribonucleotide triphosphates (dNTP), about 1 μ M of each primer and about 2.0 units Taq polymerase (available from Perkin-Elmer). This reaction mixture was created after attempts using published methods failed. Moreover, 20 additional cycles of PCR using about 5 μ l of the first round PCR sample as template under identical conditions were needed to obtain useful second round PCR product. No PCR products were identified after 30 cycles. Second round PCR products were resolved by loading about 15 μ l of the second round PCR product onto a 1.0% agarose gel in TBE buffer and staining the gel with ethidium bromide.

No PCR product was obtained using the FR2 primer combined with the FR3A primer. Several bands of DNA were obtained using the FR2 primer combined with the FR3B primer, one of which migrated at a predicted size of about 190 base pair (bp). This band was excised, and the DNA was purified using Qiaquick gel extraction kit (available from Qiagen, Chatsworth, CA) according to the manufacturer's instructions. The purified DNA was cloned into the pCR 2.1 vector (available from Invitrogen, San Diego, CA), and used to transform DH5 α *E. coli* cells (available from Invitrogen). The transformed colonies were grown overnight in about 2 ml LB media containing about 100 μ g/ml ampicillin. Plasmid DNA was purified using BioRad's Quantum Prep™

mini-prep kit (available from BioRad, Hercules, CA). Inserted sequence in 11 different plasmid samples were subjected to DNA sequence analysis using standard sequencing methods. Three different nucleic acid sequences were obtained. The 3 different nucleic acid molecules are referred to herein as hcvb3, hcvb4 and hcvb12.

5 The sequences obtained above indicated that incomplete nucleic acid molecules were obtained using the foregoing PCR procedure. To obtain more complete clones of the PCR products, primers were designed using the nucleic acid sequences obtained above, including primer Phcvb3, having the nucleic acid sequence 5' CCA GAC CTG GGT CTT GTC G 3' (SEQ ID NO:84), primer Phcvb4, having the nucleic acid sequence
10 5' CTC TGT CCT GGG AGC TGA C 3' (SEQ ID NO:85), and primer Phcvb12, having the nucleic acid sequence 5' TTG TTT GAT CTA GAG ACT GTG 3' (SEQ ID NO:86). Each primer was then used in combination with the 5' vector primer T3 (available from available from Stratagene Cloning Systems, La Jolla, CA) to amplify PCR products representing V β genes from a canine PBL cDNA library generated in the λ Zap II vector
15 (available from Stratagene Cloning Systems, La Jolla, CA). The *C. familiaris* mitogen activated PBMC cDNA library was constructed in the Uni-ZAP \circledR XR vector (available from Stratagene Cloning Systems), using Stratagene's ZAP-cDNA \circledR Synthesis Kit and the manufacturer's protocol. The mRNA was isolated from *C. familiaris* peripheral blood mononuclear cells 4 hours after they were activated by a polyclonal activating
20 agent in culture. PCR reaction were performed using the following conditions: Taq activation was performed at about 95°C for about 10 min, about 94°C for about 30 sec., about 58°C for about 30 sec., and about 72°C for about 1 min. for about 35 cycles, then clonal extension was performed at about 72°C for about 5 min.; PCR was performed in a reaction buffer containing 50 mM KCl, 10 mM Tris-HCl, pH 8.3, 0.01% gelatin, pH 3,
25 25 mM MgCl₂, about 1 unit Amplitaq GoldTM (available from Perkin-Elmer Cetus), about 200 μ M dNTP's and about 1 μ M primer.

The resulting PCR products were gel purified, cloned and sequenced using standard methods. The resulting nucleic acid sequences were aligned with the nucleic acid sequences obtained from the first set of PCR products to obtain a more complete
30 sequence of hcvb3, hcvb4 and hcvb12. Since the PCR primers used to generate the first set of PCR products were degenerate primers, the nucleic acid sequences of hcvb3,

-69-

hcvb4 and hcvb12 at the degenerate primer sites were ambiguous. To determine the sequence in the area of the degenerate primers, PCR primers corresponding to the newly derived extreme 5' ends of the hcvb3, hcvb4 and hcvb12 nucleic acid molecules were designed. Primer 5'Phcvb3, having the nucleic acid sequence 5' ATC GGA CTC CTC
5 TGT GGT GT 3' (SEQ ID NO:87), primer 5'hcvb4, having the nucleic acid sequence 5' ACG GTG AAG GGC TAG CAC CT 3' (SEQ ID NO:88) and primer 5'hcvb12, having the nucleic acid sequence 5' GCT GAA ATG GCC ACC GGC GT 3' (SEQ ID NO:89), each were used in combination with a primer specific for a sequence in the constant region of a TCR beta chain (SED ID NO:57) in PCR reactions using the cDNA library
10 described above. The resulting PCR products were purified, cloned into PCR2.1 vector (available from Invitrogen) and sequenced using standard methods.

A. A first clone (hcV β 3) was isolated, referred to herein as nCaV β 3₃₈₁, the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:1. SEQ ID NO:1 includes the V, D and J regions of the sequenced PCR
15 product. The complement of SEQ ID NO:1 is represented herein by SEQ ID NO:3. Translation of SEQ ID NO:1 suggests that nucleic acid molecule nCaV β 3₃₈₁ encodes a TCR V β protein of about 127 amino acids, denoted herein as PCaV β 3₁₂₇, the amino acid sequence of which is presented in SEQ ID NO:2, assuming an open reading frame having a first codon spanning from nucleotide 1 through nucleotide 3 of SEQ ID NO:1
20 and a last codon spanning from nucleotide 379 through nucleotide 381 of SEQ ID NO:1. The putative signal sequence extends from nucleotide 1 to nucleotide 51 of SEQ ID NO:1. The proposed mature protein (i.e., canine TCR V β protein from which the signal sequence has been cleaved), denoted herein as PCaV β 3₁₁₀, contains about 110 amino acids, extending from residue 18 through residue 127 of SEQ ID NO:2. The nucleic
25 acid molecule encoding PCaV β 3₁₁₀ is denoted herein as nCaV β 3₃₃₀, extending from nucleotide 52 through nucleotide 381 of SEQ ID NO:1.

Comparison of nucleic acid sequence SEQ ID NO:1 with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:1 showed the most homology, i.e., about 69% identity, between SEQ ID NO:1 and a human TCR β chain gene (Genbank
30 Accession No. Z223040). Comparison of amino acid sequence SEQ ID NO:2 with amino acid sequences reported in GenBank indicates that SEQ ID NO:2 showed the

most homology, i.e., about 65% identity, between SEQ ID NO:2 and an *Ovis aries* TCR V β chain protein (Genbank Accession No. gi 2665554).

B. A second clone (hcV β 4) was isolated, referred to herein as nCaV β 4₄₀₈, the coding strand of which was shown to have a nucleic acid sequence denoted herein as
5 SEQ ID NO:4. SEQ ID NO:4 includes the V, D and J regions of the sequenced PCR product. The complement of SEQ ID NO:4 is represented herein by SEQ ID NO:6. Translation of SEQ ID NO:4 suggests that nucleic acid molecule nCaV β 4₄₀₈ encodes a TCR V β protein of about 128 amino acids, denoted herein as PCaV β 4₁₂₈, the amino acid sequence of which is presented in SEQ ID NO:5, assuming an open reading frame
10 having an initiation codon spanning from nucleotide 24 through nucleotide 26 of SEQ ID NO:4 and a last codon spanning from nucleotide 405 through nucleotide 407 of SEQ ID NO:4. The coding region encoding PCaV β 4₁₂₈ is presented herein as nCaV β 4₃₈₄, which has the nucleotide sequence SEQ ID NO:6 (the coding strand) and SEQ ID NO:7 (the complementary strand). The putative signal sequence extends from nucleotide 25
15 to nucleotide 69 of SEQ ID NO:4. The proposed mature protein (i.e., canine TCR V β protein from which the signal sequence has been cleaved), denoted herein as PCaV β 4₁₁₃, contains about 113 amino acids, extending from residue 60 through residue 128 of SEQ ID NO:5. The nucleic acid molecule encoding PCaV β 4₁₁₃ is denoted herein as nCaV β 4₃₃₉, extending from nucleotide 70 through nucleotide 408 of SEQ ID NO:4.

20 Comparison of nucleic acid sequence SEQ ID NO:4 with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:4 showed the most homology, i.e., about 75% identity, between SEQ ID NO:4 and a human TCR β chain gene (Genbank Accession No. M97713). Comparison of amino acid sequence SEQ ID NO:5 with amino acid sequences reported in GenBank indicates that SEQ ID NO:5 showed the
25 most homology, i.e., about 69% identity, between SEQ ID NO:5 and an *Ovis aries* TCR V β chain protein (Genbank Accession No. gi 2665558).

C. A third clone (hcV β 12) was isolated, referred to herein as nCaV β 12₄₀₈, the coding strand of which was shown to have a nucleic acid sequence denoted herein as
30 SEQ ID NO:9. SEQ ID NO:9 includes the V, D and J regions of the sequenced PCR product. The complement of SEQ ID NO:9 is represented herein by SEQ ID NO:11. Translation of SEQ ID NO:9 suggests that nucleic acid molecule nCaV β 12₄₀₈ encodes a

TCR V β protein of about 134 amino acids, denoted herein as PCaV β 12₁₃₄, the amino acid sequence of which is presented in SEQ ID NO:10, assuming an open reading frame having an initiation codon spanning from nucleotide 7 through nucleotide 9 of SEQ ID NO:9 and a last codon spanning from nucleotide 406 through nucleotide 408 of SEQ ID NO:9. The coding region encoding PCaV β 12₁₃₄ is presented herein as nCaV β 12₄₀₂, which has the nucleotide sequence SEQ ID NO:12 (the coding strand) and SEQ ID NO:13 (the complementary strand). The putative signal sequence extends from nucleotide 7 to nucleotide 63 of SEQ ID NO:9. The proposed mature protein (i.e., canine TCR V β protein from which the signal sequence has been cleaved), denoted herein as PCaV β 12₁₁₅, contains about 115 amino acids, extending from residue 20 through residue 134 of SEQ ID NO:10. The nucleic acid molecule encoding PCaV β 12₁₁₅ is denoted herein as nCaV β 12₃₄₅, extending from nucleotide 64 through nucleotide 408 of SEQ ID NO:9.

Comparison of nucleic acid sequence SEQ ID NO:9 with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:9 showed the most homology, i.e., about 72% identity, between SEQ ID NO:9 and a *Macaca mulatta* TCR β chain mRNA (Genbank Accession No. U04578). Comparison of amino acid sequence SEQ ID NO:10 with amino acid sequences reported in GenBank indicates that SEQ ID NO:10 showed the most homology, i.e., about 57% identity, between SEQ ID NO:10 and a human TCR V β protein (Genbank Accession No. I38312).

Example 2

This example describes the isolation and sequencing of two additional canine TCR V β nucleic acid molecules.

Two canine TCR V β nucleic acid molecules were PCR amplified from the canine PBL cDNA library described above in Example 1. A pair of primers was used to amplify DNA from the cDNA library. The 5' vector primer T3, described in Example 1, was used in combination with primer Phcvb21, having the nucleic acid sequence 5' CTG TTG CCC ACG TTA GAG G 3' (SEQ ID NO:90) or primer Phcvb72, having the nucleic acid sequence 5' TTA CTG AAC TGC TGC ACT G 3' (SEQ ID NO:91). PCR reaction were performed using the following conditions: Taq activation was performed at about 95°C for about 10 min., about 94°C for about 30 sec., about 60°C for about 30

-72-

sec., about 72°C for about 1 min. for about 35 cycles; then clonal extension was performed at about 72°C for about 5 min.; PCR was performed in a reaction buffer containing 50 mM KCl, 10 mM Tris-HCl, pH 8.3, 0.01% gelatin, pH 3, 3 mM MgCl₂, about 1 unit Amplitaq Gold, about 200 μM dNTP's and about 1 μM primer. The
5 resultant PCR products obtained using standard PCR conditions (e.g., Sambrook et al., *ibid.*), were gel purified, cloned and sequenced. The PCR products are referred to herein as hcvb21 or hcvb72, respectively.

The sequences obtained were compared with sequences disclosed in Ito et al., *Immunogenetics*, vol. 38, p. 60, 1993 or Takano et al., *Immunogenetics*, vol. 40, p. 246,
10 1994. The PCR products hcvb21 or hcvb72 were found to contain more 5' nucleic acid sequence than that disclosed in the above-referenced publications. To obtain more complete nucleic acid molecules containing the V, D and J regions, PCR amplification was performed using primers designed from the 5' sequence obtained from hcvb21 or hcvb72 nucleic acid molecules. Primer 5'Phcvb21, having the nucleic acid sequence 5'
15 GCT GCA GGA TTC GGC ACG AG 3' (SEQ ID NO:92) or primer 5'Phcvb72, having the nucleic acid sequence 5' TAC GAC TGT CAG CTT GGT CC 3' (SEQ ID NO:93), each were used in conjunction with a TCR beta constant region primer (SEQ ID NO:57) to amplify these sequences from mRNA prepared from canine concavalin A (ConA)-activated PBMC. The PCR products were cloned and sequenced using standard
20 methods.

A. The clone hcVβ21 was isolated, referred to herein as nCaVβ21₄₆₂, the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:19. SEQ ID NO:19 includes the V, D and J regions of the sequenced PCR product. The complement of SEQ ID NO:19 is represented herein by SEQ ID NO:21.
25 Translation of SEQ ID NO:19 suggests that nucleic acid molecule nCaVβ21₄₆₂ encodes a TCR Vβ protein of about 130 amino acids, denoted herein as PCaVβ21₁₃₀, the amino acid sequence of which is presented in SEQ ID NO:20, assuming an open reading frame having an initiation codon spanning from nucleotide 73 through nucleotide 75 of SEQ ID NO:19 and a last codon spanning from nucleotide 460 through nucleotide 462 of
30 SEQ ID NO:19. The coding region encoding PCaVβ21₁₃₀ is presented herein as nCaVβ21₃₉₀, which extends from nucleotide 73 to nucleotide 462 of SEQ ID NO:19.

-73-

The putative signal sequence extends from nucleotide 73 to nucleotide 114 of SEQ ID NO:19. The proposed mature protein (i.e., canine TCR V β protein from which the signal sequence has been cleaved), denoted herein as PCaV β 21₁₁₆, contains about 116 amino acids, extending from residue 15 through residue 130 of SEQ ID NO:19. The nucleic acid molecule encoding PCaV β 21₁₁₆ is denoted herein as nCaV β 21₃₄₈, extending from nucleotide 115 through nucleotide 462 of SEQ ID NO:19.

A comparison of SEQ ID NO:19 with the DNA sequence DTCRB21 described in Ito et al., *ibid.* indicated that SEQ ID NO:19 is 221 nucleotides longer than at the 5' end of DTCRB21. The sequences of SEQ ID NO:19 and DTCRB21 overlap by 176 nucleotides with 100% identity, corresponding to nucleotides 222 through 398 of SEQ ID NO:19. An alignment of SEQ ID NO:19 with DTCRB21 is shown in Table 1.

TABLE 1. Nucleotide Sequence Comparison of hcvb21 and DTCRB21

15	DTCRB21	-----
	SEQ ID NO:19	GCTGCAGGAT TCGGCACGAG GCGTGGTCAT ATCTATCTTG AGAGAGGTAT
	DTCRB21	-----
	SEQ ID NO:19	GGTATGAGGC CATCACCTGA AGATGCTGAT GCTTCTGCTG CTCCTGGGGC
	DTCRB21	-----
	SEQ ID NO:19	CCAGCTCTGG ACTCGGTGCC CTCGTCTTCC AGGCGCCCAG CACAATGATC
20	DTCRB21	-----
	SEQ ID NO:19	TGTAAGAGCG GAGCCACCGT GCAGATCCAG TGTCAAACAG TGGACCTTCA
	DTCRB21	-----
	SEQ ID NO:19	AGCCACAACC GTGTTTTGGT ATCGCCAGCT CCCGAAGCAG GGCCTTACCC
25	DTCRB21	TTATGGTGAC CTCTAACGTG GGCAACAGTG CTACACACGA GCAGGGGTTC
	SEQ ID NO:19	TTATGGTGAC CTCTAACGTG GGCAACAGTG CTACACACGA GCAGGGGTTC
	DTCRB21	CCTGCAGCCA AGTTCCCTGT TAACCACCCA AACCTCACGT TTTCCTCCCT
	SEQ ID NO:19	CCTGCAGCCA AGTTCCCTGT TAACCACCCA AACCTCACGT TTTCCTCCCT
	DTCRB21	GATGGTGACG AGTTCAGGTC CTGGAGACAG CGGCCTCTAC TTCTGTGGCT
	SEQ ID NO:19	GATGGTGACG AGTTCAGGTC CTGGAGACAG CGGCCTCTAC TTCTGTGGTG
30	DTCRB21	ACC...TACA GGGCGCGCGC TACGAGCAGT ATTTCGGCGC CGGCACCAGG
	SEQ ID NO:19	TTCGGGCGTA TGGTGGGAAC TCGCCCCCTCT ACTTTGGAAC AGGCACCAGG
	DTCRB21	CTCACGGTCC TC
	SEQ ID NO:19	CTCACCGTGA CA

The amino acid sequence SEQ ID NO:20 is 50 amino acids longer at the 5' end than the amino acid sequence encoded by DTCR21. An alignment of SEQ ID NO:20 with the amino acid sequence encoded by DTCR21 is shown in Table 2.

TABLE 2. Amino Acid Sequence Comparison of hcvb21 and DTCR21.

5	SEQ ID NO:20	MLMLLLLGP	SSGLGALVFQ	APSTMICKSG	ATVQIQCQTV	DLQATTVFWD
	DTCRB21	-----	-----	-----	-----	-----
	SEQ ID NO:20	RQLPKQGLTL	MVTSNVGNSA	THEQGFPAAK	FPVNHPNLTF	SSLMVTSSGP
	DTCRB21	RQLPKQGLTL	MVTSNVGNSA	THEQGFPAAK	FPVNHPNLTF	SSLMVTSSGP
10	SEQ ID NO:20	GDSGLYFCGV	RAYGGNSPLY	FGTGTRLTVT		
	DTCRB21	GDSGLYFCGY	.LQGARYEQY	FGAGTRLTVL		

The amino acid sequence SEQ ID NO:20 is 50 amino acids longer at the 5' end than the amino acid sequence encoded by DTCR21. An alignment of SEQ ID NO:20 with the amino acid sequence encoded by DTCR21 is shown in Table 2.

- Comparison of nucleic acid sequence SEQ ID NO:19 with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:19 showed the most homology, i.e., about 38% identity, between SEQ ID NO:19 and a dog TCR β chain gene (Genbank Accession No. M97510). Comparison of amino acid sequence SEQ ID NO:20 with amino acid sequences reported in GenBank indicates that SEQ ID NO:20 showed the most homology, i.e., about 60% identity, between SEQ ID NO:20 and DTCR21 protein.

- B. The clone hcV β 72 was isolated, referred to herein as nCaV β 72₄₃₈, the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:98. SEQ ID NO:98 includes the V, D and J regions of the sequenced PCR product. The complement of SEQ ID NO:98 is represented herein by SEQ ID NO:100. Translation of SEQ ID NO:98 suggests that nucleic acid molecule nCaV β 72₄₃₈ encodes a TCR V β protein of about 133 amino acids, denoted herein as PCaV β 72₁₃₃, the amino acid sequence of which is presented in SEQ ID NO:15, assuming an open reading frame having an initiation codon spanning from nucleotide 40 through nucleotide 42 of SEQ ID NO:98 and a last codon spanning from nucleotide 436 through nucleotide 438 of SEQ ID NO:98. The coding region encoding PCaV β 72₁₃₃ is presented herein as nCaV β 72₃₉₉, which has the nucleotide sequence SEQ ID NO:17 (the coding strand) and

-75-

SEQ ID NO:18 (the complementary strand). The putative signal sequence extends from nucleotide 40 to nucleotide 96 of SEQ ID NO:98. The proposed mature protein (i.e., canine TCR V β protein from which the signal sequence has been cleaved), denoted herein as PCaV β 72₁₁₄, contains about 114 amino acids, extending from residue 20 through residue 133 of SEQ ID NO:15. The nucleic acid molecule encoding PCaV β 72₁₁₄ is denoted herein as nCaV β 72₃₄₂, extending from nucleotide 142 through nucleotide 438 of SEQ ID NO:19.

A comparison of SEQ ID NO:98 with the DNA sequence DTB72 described in Takano et al., *ibid.* indicated that SEQ ID NO:98 differs substantially from the published canine TCR V β sequence. A comparison between SEQ ID NO:98 and DTB72 is shown in Table 3.

TABLE 3. Nucleotide Sequence Comparison of hcvb72 and DTB72

	DTB72					~~~~~
	SEQ ID NO:98					CACGA
15	DTB72	~~~~~	~~~~~CAGC	TTCCCAGGGC	TGCCATGGGC	TCCAGGCTTC
	SEQ ID NO:98	GGAGCGGGGA	GGCTATCAGC	TTCCCAGGGC	TGCCATGGGC	TCCAGGCTTC
	DTB72	TCTGCTGTGT	GGCCCTTTTC	TCCTGGGAGC	CGGCCCCCGT	GGAGTCTGAG
	SEQ ID NO:98	TCTGCTGTGT	GGCCCTTTGT	CTCCTGGGAG	CCGGCCCCCGT	GGAGTCTGAG
20	DTB72	GTCAATCCAAA	CTCCAAGACA	CATGATCAAA	GTCAAGAGGA	CAGACAGTGA
	SEQ ID NO:98	GTCAATCCAAA	CTCCAAGACA	CATGATCAAA	G.CAAGAGGA	CAGACAGTGA
	DTB72	CC...TGAGA	TGTCCTTATC	TCTGGACA.C	TATCTGTGTA	CTGGTACCAA
	SEQ ID NO:98	CCCTGAGATG	TTCCCTTATC	TCTGGACACC	TATCTGTGTA	CTGGTACCAA
	DTB72	CAGGCCTTGA	TGGTCCGTTT	ACCGGTTTCT	CATTTCAGT...C
	SEQ ID NO:98	CAGGCCCTG.	GGCCAGGGTC	CCCAGTTTCT	CATTTCAGTAT	TACAATAGGG
25	DTB72	ATCATAGTCA	AAAAAGAAAC	ATCCGGTCAA	GATTCTCAGT	GCAGCAGTTC
	SEQ ID NO:98	AAGAGAGAGA	CAAAGGAGAC	ATCCCGGCAA	GATTCTCAGT	GCAGCAGTTC
	DTB72	AGTAACTACA	GCATCCCAGC	TTGAGATGAA	CTCCCTGGAG	CCAGGAGACT
	SEQ ID NO:98	AGTAACTACA	GC.TCCCAGC	TGGAGATGAA	CTCCCTGGAG	CCAGGAGACT
30	DTB72	CAGCCCTATA	TCTCTGTGCC	AGCAGC...G	GGTACAGTGA	GAGCTACGAG
	SEQ ID NO:98	CAGCCCTATA	TCTCTGTGCC	AGCAGCTTAG	ATGCGTTTCA	CGCGGGGCAG
	DTB72	CGGTATTTTCG	GAGCCGGCAC	CAGGCTCACG	GTCTTC	
	SEQ ID NO:98	CTGTACTTCG	GGGCCGGTTC	CAAGCTGGCC	GTGCTG	

Comparison of SEQ ID NO:98 with DTB72 indicates that the identity between the two sequences is about 90%, when determined using the Compare function by maximum matching within the program DNAsis™ Version 2.1. A comparison of the amino acid

sequence SEQ ID NO:15 and the amino acid sequence encoded by DTB72 indicates that the identity between the two sequences is only 57%, when determined using the Compare function by maximum matching within the program DNAsis™ Version 2.1. An alignment of the two sequences is shown in Table 4.

5 TABLE 4. Amino Acid Sequence Comparison of hcvb72 and DTB72

SEQ ID NO:15	MGSRLLCVVA	LCLLGAGPVE	SEVIQTTPRHM	IKARGQTVTL	RCSLISGHLs
DTB72	MGSRLLCVVA	LFSWEPAPVE	SEVIQTTPRHM	IKVKRTDSDL	RCPYL.WTLS
SEQ ID NO:15	VYWYQQAL.G	QGPRFLIQYY	NREERDKGDI	PARFSVQQFS	NYSSQLEMNS
10 DTB72	VYWYQQALMV	RLPVSHSVII	VKKETSGQDS	QCSSSV....	TTASQLEMNS
SEQ ID NO:15	LEPGDSALYL	CASSLDAFDA	GQLYFGAGSK	LAVL	
DTB72	LEPGDSALYL	CASS.GYSES	YERYFGAGTR	LTVL	

The comparison of the two sequences indicates that SEQ ID NO:98 and DTB72 encode
15 different proteins.

Comparison of nucleic acid sequence SEQ ID NO:19 with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:19 showed the most homology, i.e., about 60% identity, between SEQ ID NO:19 and a feline leukemia virus transduced TCR β chain gene (Genbank Accession No. X05155). Comparison of amino
20 acid sequence SEQ ID NO:20 with amino acid sequences reported in GenBank indicates that SEQ ID NO:20 showed the most homology, i.e., about 65% identity, between SEQ ID NO:20 and a a feline leukemia virus transduced TCR β chain protein (Genbank Accession No. RWMVTV).

Example 3

25 This example describes the production of two canine TCR V β nucleic acid molecules.

Two canine TCR V β nucleic acid molecules were PCR amplified from the canine PBL cDNA library described above in Example 1. A pair of primers was used to amplify DNA from the cDNA library. The 5' vector primer T3, described in Example
30 1, was used in combination with primer Pdtb54, having the nucleic acid sequence 5' CTT TTG CTG GGA TCT GCT GA 3' (SEQ ID NO:94) or primer Pdtb182, having the nucleic acid sequence 5' CAG TTG CTT AG GTC TTG CT 3' (SEQ ID NO:95). The resultant PCR products obtained using standard PCR conditions (e.g., Sambrook et al.,

-77-

ibid.), were gel purified, cloned and sequenced. The PCR products are referred to herein as dtb54 or dtb182, respectively.

The sequences obtained were compared with sequences disclosed in Takano et al., *ibid.* The PCR products dtb54 or dtb182 were found to contain more 5' nucleic acid sequence than that disclosed in the above-referenced publication. To obtain more complete nucleic acid molecules containing the V, D and J regions, PCR amplification was performed using primers designed from the 5' sequence obtained from dtb54 or dtb182 nucleic acid molecules. Primer 5'Pdtb54, having the nucleic acid sequence 5' CAC GAG CCT GCC ATG TGC CC 3' (SEQ ID NO:96) or primer 5'Pdtb182, having the nucleic acid sequence 5' GGC ACG AGC ACT GAG GAC CA 3' (SEQ ID NO:97), each were used in conjunction with a TCR beta constant region primer (SEQ ID NO:57) to amplify these sequences from mRNA prepared from canine concavalin A (ConA) activated PBMC. The PCR products were cloned and sequenced using standard methods.

15 A. The clone dtb54 was isolated, referred to herein as nCaV β 54₄₁₇, the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:22. SEQ ID NO:22 includes the V, D and J regions of the sequenced PCR product. The complement of SEQ ID NO:22 is represented herein by SEQ ID NO:24. Translation of SEQ ID NO:22 suggests that nucleic acid molecule nCaV β 54₄₁₇ encodes a
20 TCR V β protein of about 135 amino acids, denoted herein as PCaV β 54₁₃₅, the amino acid sequence of which is presented in SEQ ID NO:23, assuming an open reading frame having an initiation codon spanning from nucleotide 13 through nucleotide 15 of SEQ ID NO:22 and a last codon spanning from nucleotide 415 through nucleotide 417 of SEQ ID NO:22. The coding region encoding PCaV β 54₁₃₅ is presented herein as
25 nCaV β 54₄₀₅, which extends from nucleotide 13 to nucleotide 417 of SEQ ID NO:22. The putative signal sequence extends from nucleotide 13 to nucleotide 69 of SEQ ID NO:22. The proposed mature protein (i.e., canine TCR V β protein from which the signal sequence has been cleaved), denoted herein as PCaV β 54₁₁₆, contains about 116 amino acids, extending from residue 20 through residue 135 of SEQ ID NO:22. The
30 nucleic acid molecule encoding PCaV β 54₁₁₆ is denoted herein as nCaV β 54₃₄₈, extending from nucleotide 70 through nucleotide 417 of SEQ ID NO:22.

A comparison of SEQ ID NO:22 with the DNA sequence DTB54 described in Takano et al., *ibid.* indicated that the sequences are substantially similar except for 12 additional nucleotides at the 5' end and an additional amino acid at residue 55 in SEQ ID NO:22.

- 5 B. The clone dtb182 was isolated, referred to herein as nCaV β 182₄₂₃, the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:25. SEQ ID NO:25 includes the V, D and J regions of the sequenced PCR product. The complement of SEQ ID NO:25 is represented herein by SEQ ID NO:27. Translation of SEQ ID NO:25 suggests that nucleic acid molecule nCaV β 182₄₂₃ encodes
- 10 a TCR V β protein of about 128 amino acids, denoted herein as PCaV β 182₁₂₈, the amino acid sequence of which is presented in SEQ ID NO:26, assuming an open reading frame having an initiation codon spanning from nucleotide 40 through nucleotide 43 of SEQ ID NO:25 and a last codon spanning from nucleotide 421 through nucleotide 423 of SEQ ID NO:25. The coding region encoding PCaV β 182₁₂₈ is presented herein as
- 15 nCaV β 182₃₈₄, which extends from nucleotide 40 to nucleotide 423 of SEQ ID NO:25. The putative signal sequence extends from nucleotide 40 to nucleotide 96 of SEQ ID NO:25. The proposed mature protein (i.e., canine TCR V β protein from which the signal sequence has been cleaved), denoted herein as PCaV β 182₁₀₉, contains about 109
- 20 amino acids, extending from residue 20 through residue 128 of SEQ ID NO:25. The nucleic acid molecule encoding PCaV β 182₁₀₉ is denoted herein as nCaV β 182₃₂₇, extending from nucleotide 97 through nucleotide 423 of SEQ ID NO:25.

A comparison of SEQ ID NO:25 with the DNA sequence DTB182 described in Takano et al., *ibid.* indicated that the sequences are substantially similar except for 84 additional nucleotides at the 5' end of SEQ ID NO:25.

25 Example 4

This example describes the identification of unique TCR V β sequences by designing PCR primers that distinguish between different (TCR) V β nucleic acid molecules.

- 30 Seven different primers for PCR reactions were designed to amplify DNA from seven different TCR V β nucleic acid molecules. The primers were designed based on

the nucleic acid sequences SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:9, SEQ ID NO:98, SEQ ID NO:19, SEQ ID NO:22 or SEQ ID NO:25. The inventors discovered unique sequences for each of the foregoing nucleic acid molecules that are not shared between each of the different molecules. In addition, the inventors discovered which

5 primers designed based on those unique sequences, and under what specific conditions, did not cross-prime between the different nucleic acid molecules. For some V β genes, several different V β primers to unique sequences had to be tested in order to find one that was specific to only one V β gene. Some of the primers that were designed include:

10 primer hcV β 3 unique, having the nucleic acid sequence 5' CGA CAA GAC CCA GGT CTG G 3' (SEQ ID NO:50), complementary to nucleotides 157 to 175 of SEQ ID NO:1; primer hcV β 4 unique, having the nucleic acid sequence 5' GTC AGC TCC CAG GAC AGA G

15 3' (SEQ ID NO:51), complementary to nucleotides 176 to 194 of SEQ ID NO:4; primer hcV β 12 unique, having the nucleic acid sequence 5' CAT GAC CTG GGA CAT GGG C 3' (SEQ ID NO:52), complementary to nucleotides 172 to 190 of SEQ ID NO:9; primer hcV β 72 unique, having the nucleic acid sequence 5' GAG ATG TTC CCT TAT CT CTGG 3' (SEQ ID NO:53), complementary to nucleotides 201 to 226 of SEQ ID NO:98; primer hcV β 21 unique, having the nucleic acid sequence 5' CCT CTA ACG TGG GCA ACA G 3' (SEQ ID NO:54), complementary to nucleotides 260 to 278 of

20 SEQ ID NO:19; primer dtb54 unique, having the nucleic acid sequence 5' TCA GCA GAT CCC AGC AAA AG 3' (SEQ ID NO:55), complementary to nucleotides 174 to 193 of SEQ ID NO:22; and primer dtb182 unique, having the nucleic acid sequence 5' AGC AAG ACC TCA AGC AAC TG 3' (SEQ ID NO:56), complementary to nucleotides 203 to 222 of SEQ ID NO:25.

25 The ability of each primer to specifically prime a specific TCR V β gene was tested by performing PCR reactions using each of the above primers in combination with a V β constant region primer including: primer C β 1, having the nucleic acid sequence 5' GTG ACC TTC TGC AGA TCC TC 3' (SEQ ID NO:57); primer C β 2, having the nucleic acid sequence 5' AGC TCA GCT CCA CGT GGT C 3' (SEQ ID

-80-

NO:58); or primer C β 3, having the nucleic acid sequence 5' TGC TGA ACC CAC TCG TGA C 3' (SEQ ID NO:59).

The specificity of these primers was first tested using 7 different DNA plasmids that contained nucleic acid molecules comprising either SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:9, SEQ ID NO:98, SEQ ID NO:19, SEQ ID NO:22 or SEQ ID NO:25 as
5 templates for different PCR reaction. Each unique V β primer was used to amplify DNA from each template. PCR reactions were performed using the following conditions: Taq activation was performed at about 95°C for about 10 min., about 94°C for about 30 sec., about 60°C for about 30 sec., about 72°C for about 1 min. for about 35 cycles; then
10 clonal extension was performed at about 72°C for about 5 min.; PCR was performed in a reaction buffer containing 50 mM KCl, 10 mM Tris-HCl, pH 8.3, 0.01% gelatin, pH 3, 3 mM MgCl₂, about 1 unit Amplitaq Gold, about 0.1 μ M dNTP's and about 0.4 μ M primer. The results indicated that PCR products were only present when the correct template and primer combination was used. As such, only PCR products were present
15 when primer hcV β 3 unique was used with a plasmid containing SEQ ID NO:1, primer hcV β 4 unique was used with a plasmid containing SEQ ID NO:4, primer hcV β 12 unique was used with a plasmid containing SEQ ID NO:9, primer hcV β 72 unique was used with a plasmid containing SEQ ID NO:98, primer hcV β 21 unique was used with a plasmid containing SEQ ID NO:19, primer dtb54 unique was used with a plasmid
20 containing SEQ ID NO:22 or primer dtb182 unique was used with a plasmid containing SEQ ID NO:25.

The ability of the V β unique primers to prime DNA of the predicted size for different V β genes using cDNA from a canine ConA activated T cell population as template material was tested. The same primers and PCR amplification conditions
25 described immediately above were used in these experiments. The resulting PCR products were resolved by electrophoresis on an about 1.2% LE agarose gel in TBE buffer and stained with ethidium bromide. The results shown in Fig. 1A indicated that all seven V β unique primers were able to prime DNA fragments of the correct size. To confirm that only a specific V β gene was amplified by each V β primer, the DNA bands
30 shown in Fig. 1A were extracted from the gel and cloned. Different clones containing

DNA from the different bands were sequenced. The sequencing results indicated that each V β unique primer correctly primed only one V β gene containing sequence complementary to that primer.

Example 5

5 This example describes a method for identifying T cell expansion.

About 10^5 lymph node cells or PBMC were isolated from 2 dogs known to have lymphoma (Haynes and Stoll) and a control dog. cDNA samples from the cells were used as templates in separate PCR reactions using primer hcV β 3 unique, primer hcV β 4 unique, primer hcV β 12 unique, primer hcV β 72 unique, primer hcV β 21 unique, primer dtb54 unique or primer dtb182 unique, in combination with C β 3 primer (SEQ ID NO:59). PCR reactions were performed using the following conditions: Taq activation was performed at about 95°C for about 10 min., about 94°C for about 30 sec., about 60°C for about 30 sec., about 72°C for about 1 min. for about 35 cycles; then clonal extension was performed at about 72°C for about 5 min.; PCR was performed in a reaction buffer containing 50 mM KCl, 10 mM Tris-HCl, pH 8.3, 0.01% gelatin, pH 3, 3 mM MgCl₂, about 1 unit Amplitaq Gold, about 0.1 μ M dNTP's and about 0.4 μ M primer. PCR products were resolved by electrophoresis on an about 1.2% LE agarose gel in TBE buffer and stained with ethidium bromide.

The results shown in Fig. 1A indicated that PCR products using cells isolated from the control dog were generated using all 7 V β specific primers. In addition, the levels of PCR products were substantially the same using the 7 V β specific primers. The results shown in Fig. 1B and 1C indicated that the V β profiles of PCR products using cells isolated from the lymphoma dog Haynes, or the lymphoma dog Stoll, were different from the V β profile of the control dog. In particular, T cells expressing hcV β 21 genes have been expanded in both patients, while T cells expressing the other 6 V β genes have decreased in proportion.

Taken together, the results disclosed in Examples 3 and 4 indicate that primers complementary to unique V β sequences of the present invention can be used to: (1) detect the presence of specific V β genes in a population of cells; (2) identify clonal expansion of cells expressing a particular V β gene; and (3) associate clonal T cell

expansion with an abnormal state or disease; or (4) distinguish a general lymphoproliferative state involving polyclonal T cell activation from clonal T cell expansion.

Example 6

- 5 This example describes a method for DNA fingerprinting the junctional regions of rearranged V β genes to identify clonal expansion of T cells.

DNA sequence analysis of the junction between the V, D and J regions of a V β gene can determine whether a mRNA population that translates into a V β protein is homogenous or heterogeneous by looking at the fluorescent DNA fingerprint.

- 10 Fluorescent DNA fingerprints of V β mRNA populations were determined as follows. cDNA was prepared using standard methods from mitogen stimulated canine PBL cells isolated from a control dog and from lymph node cells isolated from the lymphoma dog Haynes or. The cDNA samples from either Haynes or the control dog were used as templates for PCR reactions using variable region primers in combination with constant
15 region primers. Use of such primers were designed so that the resulting PCR products span the D/J junction of a V β cDNA. Primer hcV β 3 unique, primer hcV β 4 unique, primer hcV β 12 unique, primer hcV β 72 unique, primer hcV β 21 unique, primer dtb54
unique or primer dtb182 unique, was used in combination with the C β 3 primer (SEQ ID NO:59). PCR reactions were performed using the following conditions: Taq activation
20 was performed at about 95°C for about 10 min., about 94°C for about 30 sec., about 60°C for about 30 sec., about 72°C for about 1 min. for about 35 cycles; then clonal extension was performed at about 72°C for about 5 min.; PCR was performed in a reaction buffer containing 50 mM KCl, 10 mM Tris-HCl, pH 8.3, 0.01% gelatin, pH 3, 3 mM MgCl₂, about 1 unit Amplitaq Gold, about 0.1 μ M dNTP's and about 0.4 μ M
25 primer.

- About 20-25 μ l of each resulting PCR product was resolved by electrophoresis on an about 1.2% LE agarose gel in TBE buffer and stained with ethidium bromide. DNA bands of about 400 bp identified on the gel were excised and the DNA purified. The purified DNA was sequenced using the C β 2 primer (SEQ ID NO:58) using standard
30 fluorescent dyes and an automated DNA sequencer.

Fluorescent electrophoretic histograms were generated for sequence obtained using each primer and each template. Fig. 2 illustrates 7 histograms generated using cDNA from the control dog and each of the 4 V β primers. The histograms show the typical heterogeneity of a T cell population in a normal dog. These histograms indicate
5 that the DNA sequences of a particular amplified V β PCR product can be determined through the first about 120 bp of the V β constant region, but become ambiguous as the sequence profile enters the heterogenous J/D junctional regions.

Fig. 3 illustrates 4 histograms generated using cDNA from the lymphoma dog Haynes and V β primers hcV β 12 unique, hcV β 72 unique, hcV β 21 unique, dtb54 unique
10 or dtb182 unique. The histograms show that 3 of the 4 V β genes amplified have fingerprints similar to those seen with a heterogeneous population of T cells, such as shown in Fig. 2. The histogram generated using the hcvb21 unique primer has a fingerprint which allows the unambiguous determination of the DNA sequence throughout the entire junctional region between the V, D, J and C regions. This result
15 indicates that the sequence recognized by the hcvb21 unique primer was dominant among the canine PBL cell population from the lymphoma dog.

A comparison of the histogram generated using the hcvb21 unique primer with cDNA from the normal dog with the histogram generated using the hcvb21 unique primer with cDNA from the lymphoma dog is shown in Fig. 4. The comparison
20 illustrates that the difference between the two histograms can be used to determine clonal expansion of a single T cell and association of such expansion to an abnormal state or disease.

Example 7

This example describes the generation of T cell clones reactive to flea saliva
25 allergens, and the characterization of the TCR V β genes used by the T cell receptors of the T cell clones.

It is to be noted that this example includes a number of cellular immunology techniques considered to be familiar to those skilled in the art. Disclosure of such techniques can be found, for example, in Coligan et al., *Current Protocol in*
30 *Immunology*, Wiley Interscience, New York. T cell clones reactive to flea saliva

antigens were generated from peripheral blood mononuclear cells (PBMC) isolated from the experimentally-induced flea allergic dog CPO2 (described in U.S. Patent No. 5,646,115, issued on July 8, 1997) as follows. Blood samples were isolated from experimentally-induced flea allergic dog CPO2. Peripheral blood lymphocytes (PBL) were harvested from each sample by centrifugation using a ficoll gradient (available from Pharmacia). The PBL cells were cultured in about 5 ml cultures in culture medium containing IMDM and 10% fetal calf serum (available from Gibco, Gaithersburg, MD) at about 5×10^6 cells/ml in the presence of about $5 \mu\text{g/ml}$ flea saliva protein (prepared according to the methods described in U.S. Patent No. 5,646,115) for about 14 days, at about 37°C , in about 5% CO_2 . The incubated cells were harvested and the number of viable cells determined. The viable cells were plated in 96 well round bottom plates at about 10^2 or about 10^3 cells per well per $200 \mu\text{l}$ of culture medium in the presence of about 10^5 autologous irradiated PBL (prepared according to the methods generally described in Coligan, *ibid.*) as antigen presenting cells (APC), about $5 \mu\text{g/ml}$ of flea saliva protein, and about 10 units/ml of recombinant hIL-2 for another 14 days. Wells that contain growing cells were restimulated *in situ* by replacing about $150 \mu\text{l}$ of spent culture medium (i.e., medium in which cells had been grown) with about $150 \mu\text{l}$ of fresh culture medium, flea saliva protein and APC as described above. About 10-14 days later, cultures in which the T cells were actively proliferating were transferred into 48 well plates, and tested for antigen specificity by comparing growth of the cells in the presence of flea saliva protein and APC, with growth of cells in the presence of APC alone. Cells that required flea saliva protein and APC to grow were selected and expanded in the presence of APC and flea saliva protein. These expanded cells are referred to as T cell clones.

Seven different T cell clones were derived from cells isolated from CPO2. mRNA was prepared from about 10^6 cells from each of the 7 clones using standard methods. cDNA was prepared from the mRNA using methods described above in Example 1. The cDNA samples from the 7 clones were then used as templates in PCR reactions to determine the presence of particular TCR V β molecules using the methods described above in Example 4. Analysis of the resulting PCR products indicated that 6

of the 7 clones expressed TCR using the dtb182 V beta chain, thereby indicating a bias in TCR V β usage in the T cell reactivity of CPO2 to flea saliva protein.

While various embodiments of the present invention have been described in detail, it is apparent that modifications and adaptations of those embodiments will occur to those skilled in the art. It is to be expressly understood, however, that such
5 modifications and adaptations are within the scope of the present invention, as set forth in the following claims.

What is claimed is:

1. An isolated protein comprising a protein selected from the group consisting of:

(a) an isolated protein having an amino acid sequence that is at least
5 about 55 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:29, SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 amino acids in length;

(b) an isolated protein having an amino acid sequence that is at least
10 about 75 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:32, SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 15 amino acids in length;

(c) an isolated protein having an amino acid sequence that is at least
15 about 50% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:10, SEQ ID NO:35, SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 25 amino acids in length; and

(d) an isolated protein having an amino acid sequence that is at least
about 50% identical to an amino acid sequence selected from the group consisting of
SEQ ID NO:15, SEQ ID NO:38, SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71,
or a fragment thereof that is at least about 35 amino acids in length.

20 2. An isolated protein comprising a protein selected from the group consisting of:

(a) a protein encoded by a nucleic acid molecule that is at least about
70 percent identical to a nucleic acid sequence selected from the group consisting of
SEQ ID NO:1, SEQ ID NO:28, SEQ ID NO:50, and a nucleic acid sequence that
25 encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60,
SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25
nucleotides in length;

(b) a protein encoded by a nucleic acid molecule that is at least about
75 percent identical to a nucleic acid sequence selected from the group consisting of
30 SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:31, SEQ ID NO:51, and a nucleic acid
sequence that encodes an amino acid sequence selected from the group consisting of

SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment that is at least about 30 nucleotides in length;

(c) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of
5 SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:34, SEQ ID NO:52, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 40 nucleotides in length; and

(d) a protein encoded by a nucleic acid molecule that is at least about
10 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:17, SEQ ID NO:37, SEQ ID NO:53, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 75 nucleotides in length.

15 3. An isolated nucleic acid molecule having a nucleic acid sequence that is selected from the group consisting of:

(a) a nucleic acid sequence that is at least about 70 percent identical
to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:28, SEQ ID NO:30 and a nucleic acid sequence that encodes an
20 amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 nucleotides in length;

25 (b) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:31, SEQ ID NO:33, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of
30 SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of

SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 30 nucleotides in length;

(c) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:34, SEQ ID NO:36, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:67, or a fragment thereof that is at least about 40 nucleotides in length;

(d) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:37, SEQ ID NO:39, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 75 nucleotides in length; and

(e) a nucleic acid sequence selected from the group consisting of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, and SEQ ID NO:56.

4. An isolated nucleic acid molecule selected from the group consisting of:

(a) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:28, and SEQ ID NO:30, or a fragment thereof, wherein said fragment has at least a 20 contiguous nucleotide region identical in sequence to a 20 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:28, and SEQ ID NO:30;

(b) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:31, and SEQ ID NO:33, or a fragment thereof,

wherein said fragment has an at least a 25 contiguous nucleotide region identical in sequence to a 25 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:31 and SEQ ID NO:33;

- 5 (c) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:34, and SEQ ID NO:36, or a fragment thereof, wherein said fragment has an at least a 30 contiguous nucleotide region identical in sequence to a 30 contiguous nucleotide region of a nucleic acid sequence selected from
10 the group consisting of SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:34, and SEQ ID NO:36; and

- (d) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:37, and SEQ ID NO:39, or a fragment thereof,
15 wherein said fragment has an at least a 60 contiguous nucleotide region identical in sequence to a 60 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:37, and SEQ ID NO:39.

-
5. An isolated nucleic acid molecule having a nucleic acid sequence
20 encoding a protein selected from the group consisting of:
- (a) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:28, SEQ ID NO:50, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60,
25 SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 nucleotides in length;

- (b) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:31, SEQ ID NO:51, and a nucleic acid
30 sequence that encodes an amino acid sequence selected from the group consisting of

-90-

SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 30 nucleotides in length;

(c) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of
 5 SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:34, SEQ ID NO:52, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 40 nucleotides in length; and

(d) a protein encoded by a nucleic acid molecule that is at least about
 10 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:17, SEQ ID NO:37, SEQ ID NO:53, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 75 nucleotides in length.

15 6. An isolated oligonucleotide comprising a unique nucleic acid sequence within a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ
 20 ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID
 25 NO:56, complements of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID
 30 NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID

- 91 -

NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, and SEQ ID NO:80; and a homolog thereof.

7. A reagent that is unique to a nucleic acid molecule selected from the group consisting of nCaV β 3₃₈₁, nCaV β 4₄₀₈, nCaV β 4₃₈₄, nCaV β 12₄₀₈, nCaV β 12₄₀₂,
 5 nCaV β 72₄₃₈, nCaV β 72₃₉₉, nCaV β 3₃₃₃, nCaV β 4₃₅₁, nCaV β 12₃₃₉, nCaV β 72₄₂₃,
 nCaV β 21₃₉₆, nCaV β 54₃₅₄ and nCaV β 182₃₆₉, wherein said reagent can distinguish one member of said group from another member of said group.

8. A method to detect expansion of T cells in an animal comprising:

(a) identifying the presence of one or more T cell receptor nucleic
 10 acid molecule(s) having unique nucleic acid sequences within variable regions of beta chain nucleic acid molecules selected from the group consisting of nCaV β 3₃₈₁,
 nCaV β 4₄₀₈, nCaV β 4₃₈₄, nCaV β 12₄₀₈, nCaV β 12₄₀₂, nCaV β 72₄₃₈, nCaV β 72₃₉₉, nCaV β 3₃₃₃,
 nCaV β 4₃₅₁, nCaV β 12₃₃₉, nCaV β 72₄₂₃, nCaV β 21₃₉₆, nCaV β 54₃₅₄ and nCaV β 182₃₆₉ by forming detectable products; and
 15 (b) detecting the expansion of said T cells by determining production of said product.

9. A therapeutic composition that, when administered to an animal,

regulates an immune response in said animal, said therapeutic composition comprising a therapeutic compound selected from the group consisting of:

20 (i) an isolated protein comprising a TCR V β protein selected from the group consisting of:

(a) an isolated protein having an amino acid sequence that is at least about 55 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:29, SEQ ID NO:60, SEQ ID NO:61, and SEQ
 25 ID NO:62, or a fragment thereof that is at least about 25 amino acids in length;

(b) an isolated protein having an amino acid sequence that is at least about 75 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:32, SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 15 amino acids in length;

30 (c) an isolated protein having an amino acid sequence that is at least about 50% identical to an amino acid sequence selected from the group

- 92 -

consisting of SEQ ID NO:10, SEQ ID NO:35, SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 25 amino acids in length; and

- (d) an isolated protein having an amino acid sequence that is at least about 50% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:15, SEQ ID NO:38, SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 35 amino acids in length;

- (ii) a mimotope of any of said TCR V β proteins;
- (iii) a chimeric form of any of said TCR V β proteins;
- (iv) an isolated nucleic acid molecule selected from the group

10 consisting of:

- (a) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:28, SEQ ID NO:30 and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 nucleotides in length;

- (b) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:31, SEQ ID NO:33, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 30 nucleotides in length;

- (c) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:34, SEQ ID NO:36, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, and the complement

-93-

of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:67, or a fragment thereof that is at least about 40 nucleotides in length;

(d) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:37, SEQ ID NO:39, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 75 nucleotides in length; and

(e) a nucleic acid sequence selected from the group consisting of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, and SEQ ID NO:56;

(v) an isolated antibody that selectively binds to any of said TCR V β proteins; and

(vi) an inhibitor of TCR V β protein activity identified by its ability to inhibit the activity of said TCR V β proteins.

10. A method to produce a TCR V β protein, said method comprising culturing a cell capable of expressing said protein, said protein selected from the group consisting of:

(a) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:28, SEQ ID NO:50, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 nucleotides in length;

(b) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:31, SEQ ID NO:51, and a nucleic acid

- 94 -

sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment that is at least about 30 nucleotides in length;

(c) a protein encoded by a nucleic acid molecule that is at least about 5 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:34, SEQ ID NO:52, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 40 nucleotides in length; and

10 (d) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:17, SEQ ID NO:37, SEQ ID NO:53, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at 15 least about 75 nucleotides in length.

11. The invention of Claim 1, 2, 9 or 10, wherein said protein, when administered to an animal, can perform a function selected from the group consisting of eliciting an immune response against a TCR V β protein and binding to a MHC molecule that binds to a TCR V β protein.

20 12. The invention of Claim 1, 2, 9 or 10, wherein said protein is selected from the group consisting of: a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID 25 NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70 and SEQ ID NO:71; and a protein encoded by an allelic variant of a nucleic acid molecule encoding a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:60, SEQ ID NO:61, SEQ ID 30 NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70 and SEQ ID NO:71.

- 95 -

13. An isolated antibody that selectively binds to a protein as set forth in the invention of Claim 1, 2, 9 or 10.

14. The nucleic acid molecule of the invention of Claim 3-10, wherein said nucleic acid molecule comprises a nucleic acid sequence that encodes a TCR V β protein.

5 15. The nucleic acid molecule of the invention of Claim 3-10, wherein said nucleic acid molecule encodes a protein that elicits an immune response against a naturally-occurring TCR V β protein.

16. The nucleic acid molecule of the invention of Claim 3-10, wherein said nucleic acid molecule comprises a nucleic acid molecule selected from the group
10 consisting of nCaV β 3₃₈₁, nCaV β 4₄₀₈, nCaV β 4₃₈₄, nCaV β 12₄₀₈, nCaV β 12₄₀₂, nCaV β 72₄₃₈, nCaV β 72₃₉₉, nCaV β 3₃₃₃, nCaV β 4₃₅₁, nCaV β 12₃₃₉ and nCaV β 72₄₂₃.

17. The nucleic acid molecule of the invention of Claim 3-10, wherein said nucleic acid molecule is selected from the group consisting of: a nucleic acid molecule comprising a nucleic acid sequence that encodes a protein having an amino acid
15 sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70 and SEQ ID NO:71; and a nucleic acid molecule comprising an
20 allelic variant of a nucleic acid molecule encoding a protein having any of said amino acid sequences.

18. The nucleic acid molecule of the invention of Claim 3-10, wherein said nucleic acid molecule is selected from the group consisting of: a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:1,
25 SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17 and SEQ ID NO:18; and a nucleic acid molecule comprising an allelic variant of a nucleic acid molecule comprising any of said nucleic acid sequences.

19. The nucleic acid molecule of the invention of Claim 3-10, wherein said
30 nucleic acid molecule comprises an oligonucleotide.

-96-

20. A recombinant molecule comprising a nucleic acid molecule as set forth in the invention of Claim 3-10 operatively linked to a transcription control sequence.

21. A recombinant virus comprising a nucleic acid molecule as set forth in the invention of Claim 3-10.

5 22. A recombinant cell comprising a nucleic acid molecule as set forth in the invention of Claim 3-10.

23. The invention of Claim 3-10, wherein said nucleic acid molecule comprises an oligonucleotide from about 15 nucleotides to about 25 nucleotides in length.

10 24. The invention of Claim 3-10, wherein said nucleic acid molecule comprises an oligonucleotide selected from the group consisting of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and complements of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, and SEQ ID NO:56.

15 25. The invention of Claim 3-10, wherein said nucleic acid molecule has a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and complements of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, and SEQ ID NO:56.

26. The invention of Claim 3-10, wherein said invention comprises a reagent which identifies the presence of a T cell receptor having a unique nucleic acid sequence within said nucleic acid molecule.

27. The invention of Claim 3-10, wherein said invention comprises a reagent
30 which is a DNA primer complementary to said unique nucleic acid sequence.

- 97 -

28. The invention of Claim 3-10, wherein said invention comprises a unique nucleic acid sequence that is selected from the group consisting of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55 and SEQ ID NO:56.

5 29. A kit comprising said reagent of Claim 7, wherein said kit comprises one or more of said reagents and a means for detecting said reagents.

30. A kit comprising said reagent of Claim 7, wherein said kit comprises seven of said reagents, wherein each of said seven reagents identifies the presence of a different beta chain V region selected from the group consisting of nCaV β 3₃₈₁,
 10 nCaV β 4₄₀₈, nCaV β 4₃₈₄, nCaV β 12₄₀₈, nCaV β 12₄₀₂, nCaV β 72₄₃₈, nCaV β 72₃₉₉, nCaV β 3₃₃₃,
 nCaV β 4₃₅₁, nCaV β 12₃₃₉, nCaV β 72₄₂₃, nCaV β 21₃₉₆, nCaV β 54₃₅₄ and nCaV β 182₃₆₉.

31. The kit of Claim 30, wherein said kit further comprises a DNA primer complementary to a nucleic acid sequence in the constant region of a T cell receptor beta chain.

15 32. The kit of Claim 30, wherein said constant region nucleic acid sequence is selected from the group consisting of SEQ ID NO:58 and SEQ ID NO:59.

33. The kit of Claim 30, wherein said kit comprises a composition comprising a mixture of said reagents and said DNA primer complementary to a nucleic acid sequence in the constant region of a T cell receptor beta chain.

20 34. The method of Claim 8, wherein said step of detecting comprises comparing formation of one detectable product with one or more other detectable products.

35. The method of Claim 8, wherein said variable region has a nucleic acid sequence selected from the group consisting of SEQ ID NO:28, SEQ ID NO:30, SEQ ID
 25 NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID
 NO:39, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID
 NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID
 NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and complements of SEQ ID
 NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID
 30 NO:55, and SEQ ID NO:56.

36. The method of Claim 8, wherein said step of identification comprises:
- (a) contacting a sample containing DNA from T cells with a reagent having specificity for one of said unique nucleic acid sequences; and
 - (b) determining the presence of DNA carrying said unique nucleic acid sequence.
37. The method of Claim 8, wherein said reagent is a DNA primer that is complementary to said unique nucleic acid sequence.
38. The method of Claim 8, wherein said step of identification is performed using polymerase chain reaction amplification.
39. The method of Claim 8, wherein said method detects a disease that is selected from the group consisting of cancer, an autoimmune disease, an infectious disease and allergy.
40. The invention of Claim 8 or 9, wherein said animal is selected from the group consisting of an animal suspected of having a disease, an animal having a disease and an animal being treated for a disease, wherein said disease is selected from the group consisting of lymphoma, leukemia, rheumatoid arthritis, diabetes, viral infections, bacterial infections, yeast infections, parasite infections, dermatitis, and asthma.
41. The method of Claim 40, wherein said disease is selected from the group consisting of T cell lymphoma and T cell leukemia.
42. A composition comprising the invention of Claim 1, 2, 3, 4, 5, 6, or 9, wherein said composition further comprises a component selected from the group consisting of an excipient, an adjuvant and a carrier.
43. The composition of Claim 9, wherein said therapeutic compound is selected from the group consisting of a peptide, a naked nucleic acid vaccine and a recombinant cell vaccine.
44. A method to regulate an immune response in an animal comprising administering to the animal a therapeutic composition comprising the invention of Claim 1, 2, 3, 4, 5, 6, or 9.
45. A method for prescribing treatment for specific disease, comprising:
- (a) identifying the presence of a T cell receptor nucleic acid molecule having a unique nucleic acid sequence within a variable region of a beta chain nucleic

-99-

acid molecule selected from the group consisting of nCaV β 3₃₃₃, nCaV β 4₃₅₁, nCaV β 12₃₃₉, nCaV β 72₄₂₃, nCaV β 21₃₉₆, nCaV β 54₃₅₄, nCaV β 182₃₆₉, nCaV β 3₃₈₁, nCaV β 4₄₀₈, nCaV β 12₄₀₈, nCaV β 72₄₃₈, nCaV β 21₄₆₂, nCaV β 54₄₁₇ and nCaV β 182₄₂₃; and

(b) prescribing a treatment comprising administering to said animal a
5 therapeutic composition comprising the invention of Claim 1, 2, 3, 4, 5, 6, or 9.

46. The reagent of Claim 7, wherein said reagent identifies the presence of a
T cell receptor having a unique nucleic acid sequence within said nucleic acid molecule.

47. The reagent of Claim 7, wherein said reagent is a DNA primer
complementary to said unique nucleic acid sequence.

10 48. The reagent of Claim 7, wherein said unique nucleic acid sequence is
selected from the group consisting of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52,
SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55 and SEQ ID NO:56.

1/7

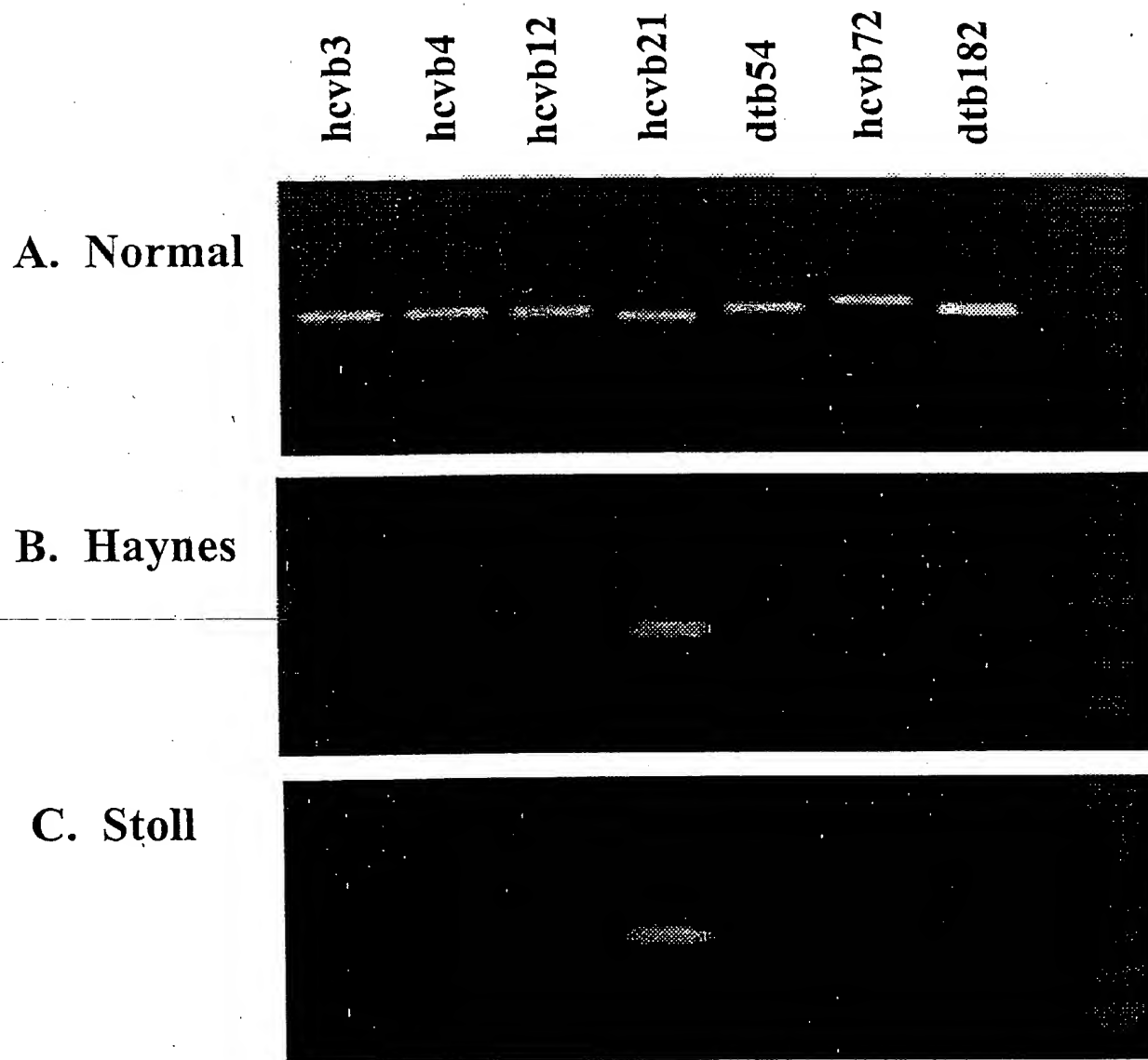
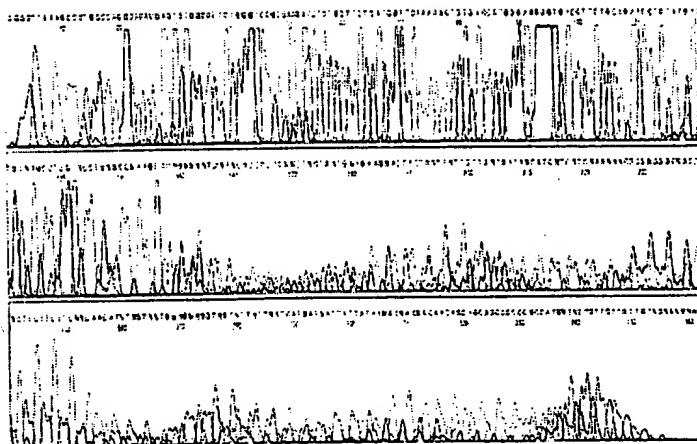


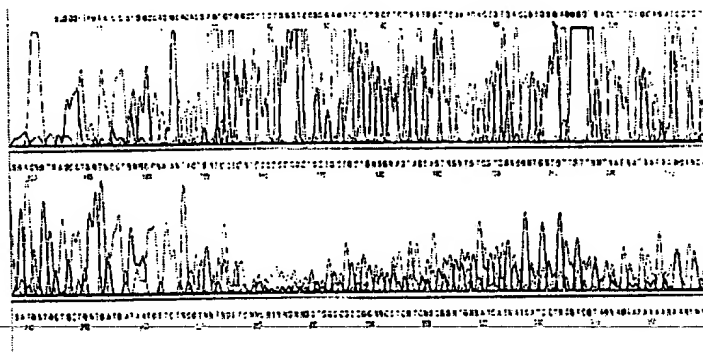
Fig. 1

2/7

hcvb3



hcvb4



hcvb12

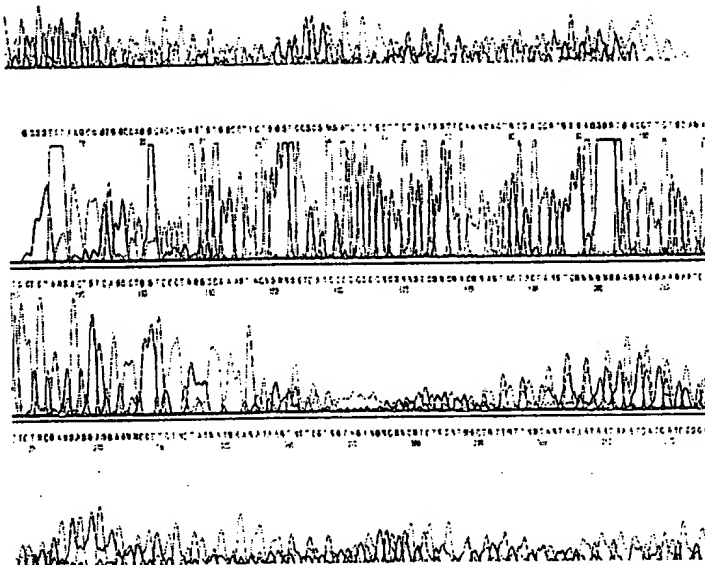
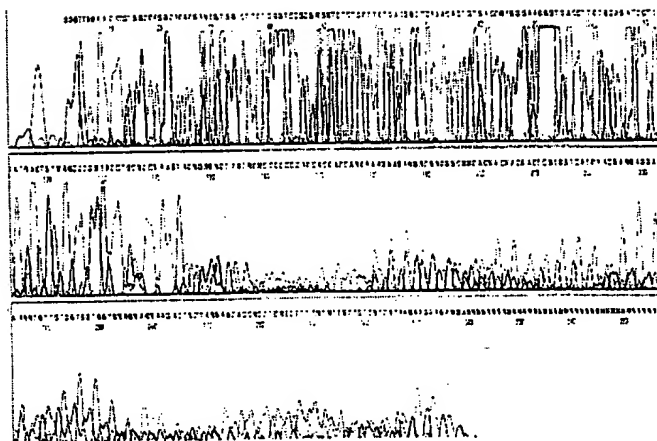


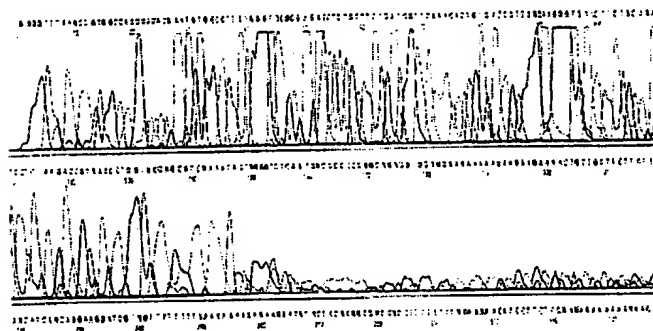
Fig. 2A

3/7

hcvb21



dtb54



hcvb72

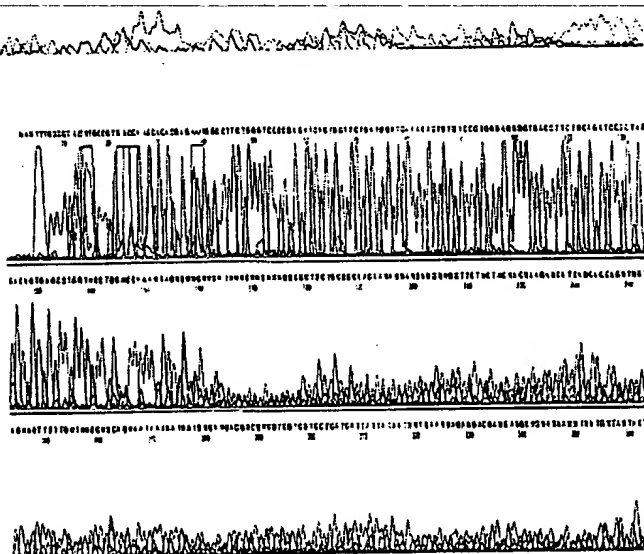


Fig. 2B

4/7

dtb182

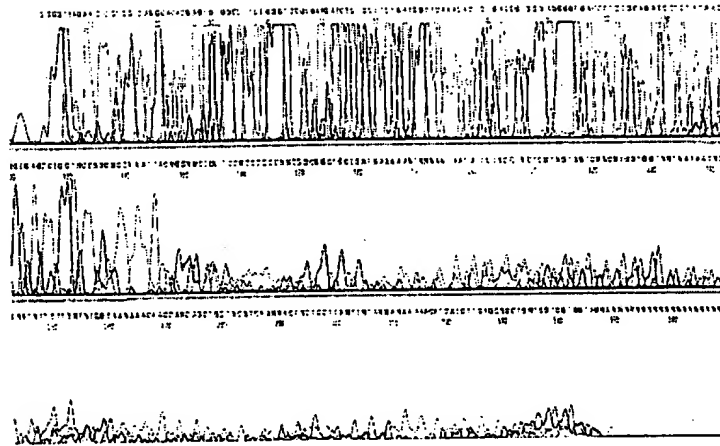
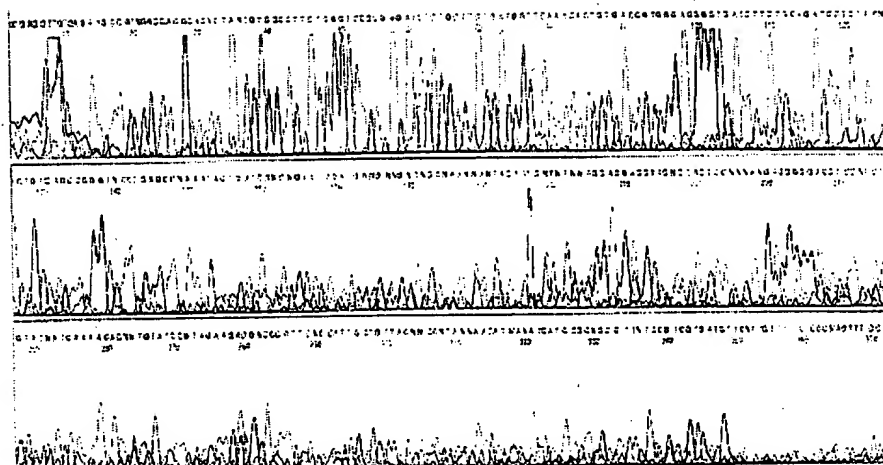


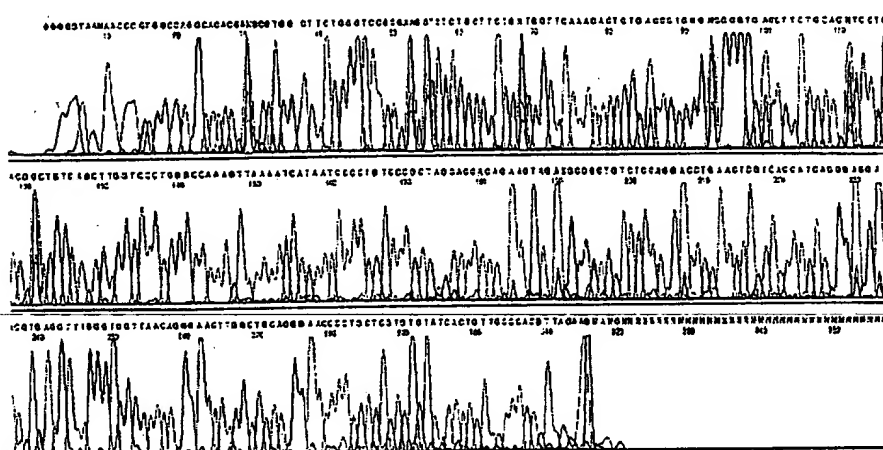
Fig. 2C

5/7

hcvb12



hcvb21



dtb54

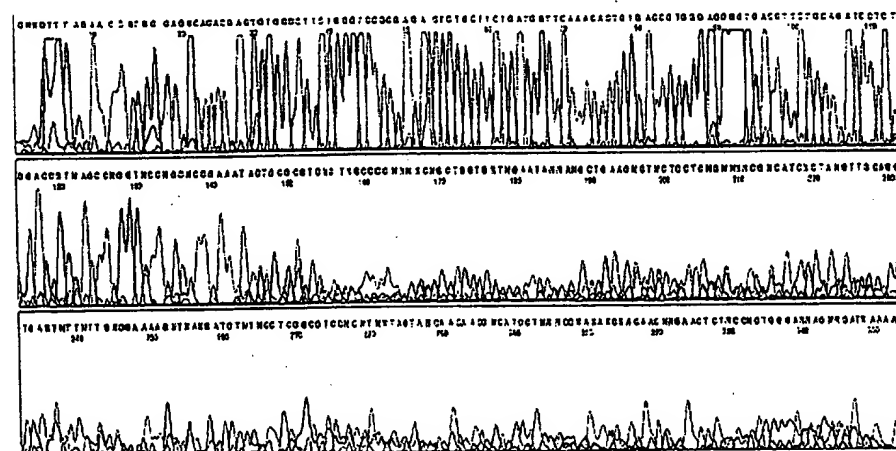


Fig. 3A

6/7

dtb182

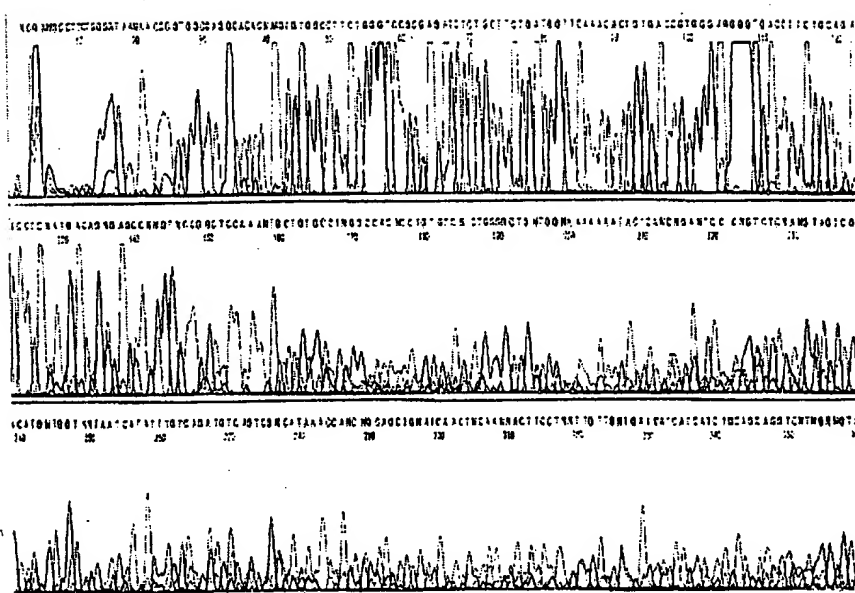
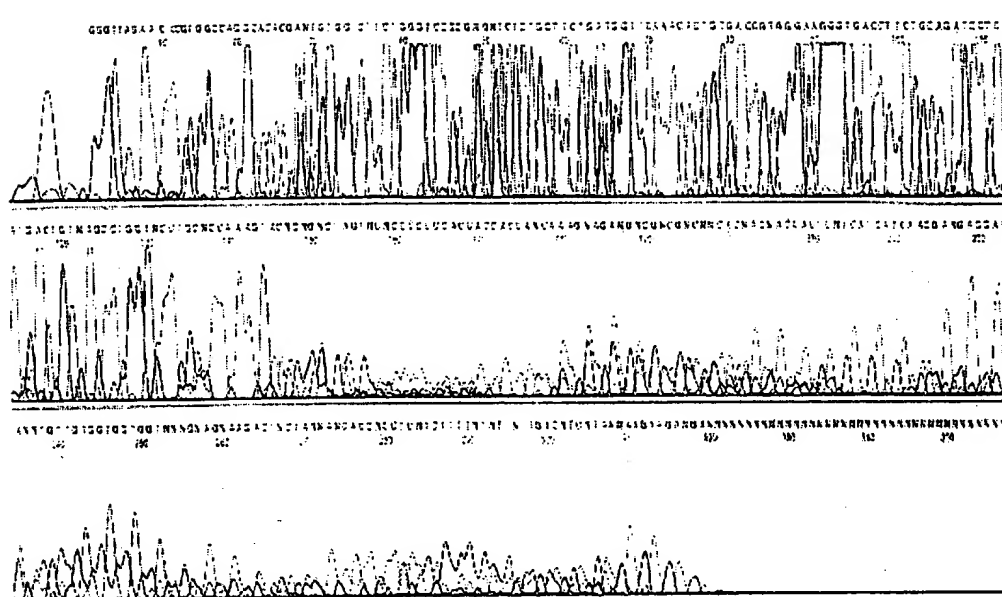


Fig. 3B

717

Normal
hcvb21



Haynes
hcvb21

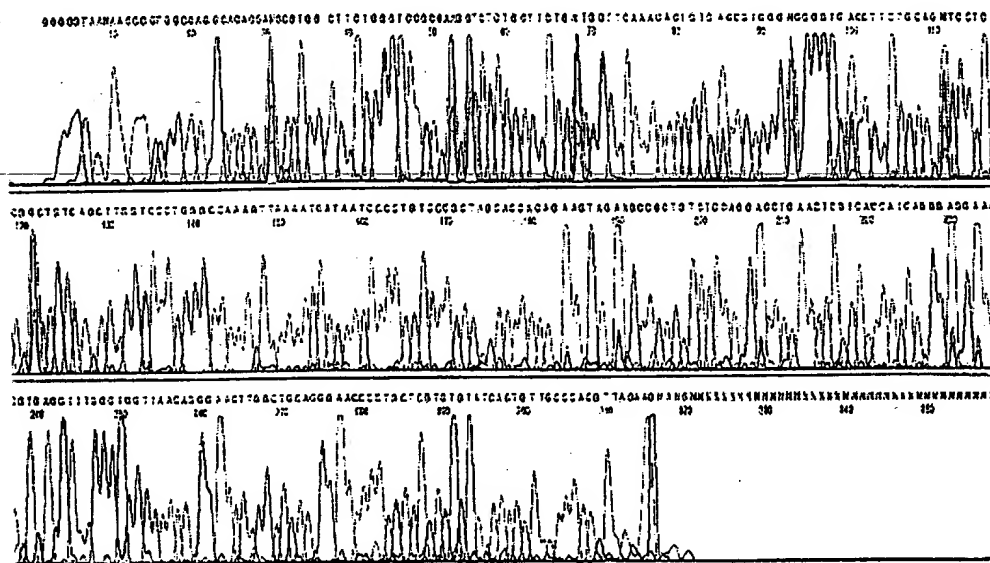


Fig. 4

SEQUENCE LISTING

<110> Sim, Gek-Kee
Dreitz, Matthew J.

<120> T CELL RECEPTOR PROTEINS, NUCLEIC ACID MOLECULES, AND
USES THEREOF

<130> IM-3-C1-PCT

<140> not yet assigned

<141> 1999-07-29

<150> 60/094,506

<151> 1998-07-29

<160> 100

<170> WordPerfect for Windows 7.0

<210> 1

<211> 381

<212> DNA

<213> Canis familiaris

<220>

<221> CDS

<222> (1)..(381)

<400> 1

atc gga ctc ctc tgt ggt gtg gcc ttt tgt ttc ctg gga gta ggc ctt 48

Ile Gly Leu Leu Cys Gly Val Ala Phe Cys Phe Leu Gly Val Gly Leu
1 5 10 15

ttg aac gca caa gtg act caa acc ccg aga caa ctc atc aaa aaa gtg 96

Leu Asn Ala Gln Val Thr Gln Thr Pro Arg Gln Leu Ile Lys Lys Val
20 25 30

gga gcg aaa gtt ttg ttg aaa tgt tca cag aat atg gac cat gaa aga 144

Gly Ala Lys Val Leu Leu Lys Cys Ser Gln Asn Met Asp His Glu Arg
35 40 45

atg ttc tgg tat cga caa gac cca ggt ctg ggg ttg cgg ctg ctc tac 192

Met Phe Trp Tyr Arg Gln Asp Pro Gly Leu Gly Leu Arg Leu Leu Tyr
50 55 60

tgg tcc tat aat att gac agt gtt gag aca gga gac atc cct tat ggg 240

Trp Ser Tyr Asn Ile Asp Ser Val Glu Thr Gly Asp Ile Pro Tyr Gly
65 70 75 80

tac agt gtc tcg agg aag aag aag gat gcc ttc ccc ttg att ctg gag 288

Tyr Ser Val Ser Arg Lys Lys Lys Asp Ala Phe Pro Leu Ile Leu Glu

	85		90		95	
tct gct cgc atc aac cag aca tct gtg tac ttc tgc gcc agc agc ccg						336
Ser Ala Arg Ile Asn Gln Thr Ser Val Tyr Phe Cys Ala Ser Ser Pro						
	100		105		110	
ttt agc caa aat acc cag tac ttc ggg gcg ggc acc cgg ctg cta						381
Phe Ser Gln Asn Thr Gln Tyr Phe Gly Ala Gly Thr Arg Leu Leu						
	115		120		125	

<210> 2
 <211> 127
 <212> PRT
 <213> Canis familiaris

<400> 2
 Ile Gly Leu Leu Cys Gly Val Ala Phe Cys Phe Leu Gly Val Gly Leu
 1 5 10 15
 Leu Asn Ala Gln Val Thr Gln Thr Pro Arg Gln Leu Ile Lys Lys Val
 20 25 30
 Gly Ala Lys Val Leu Leu Lys Cys Ser Gln Asn Met Asp His Glu Arg
 35 40 45
 Met Phe Trp Tyr Arg Gln Asp Pro Gly Leu Gly Leu Arg Leu Leu Tyr
 50 55 60
 Trp Ser Tyr Asn Ile Asp Ser Val Glu Thr Gly Asp Ile Pro Tyr Gly
 65 70 75 80
 Tyr Ser Val Ser Arg Lys Lys Lys Asp Ala Phe Pro Leu Ile Leu Glu
 85 90 95

Ser Ala Arg Ile Asn Gln Thr Ser Val Tyr Phe Cys Ala Ser Ser Pro
 100 105 110
 Phe Ser Gln Asn Thr Gln Tyr Phe Gly Ala Gly Thr Arg Leu Leu
 115 120 125

<210> 3
 <211> 381
 <212> DNA
 <213> Canis familiaris

<400> 3
 tagcagccgg gtgccccgcc cgaagtactg ggtattttgg ctaaacgggc tactggcgca 60
 gaagtacaca gatgtctggt tgatgcgagc agactccaga atcaagggga aggcattcctt 120

```
<210> 4
<211> 408
<212> DNA
<213> Canis familiaris
```

```
<220>  
<221> CDS  
<222> (25) .. (408)
```

```
<400> 4
acgggtgaagg gctagcacct aaag atg ctg act tgc ctg cta ctc ctc ctg      51
                Met Leu Thr Cys Leu Leu Leu Leu Leu
                1               5
```

gga caa ggc tct gtg ttt gga gct ctt gtc tct caa aag ccg cgc agg 99
Gly Gln Gly Ser Val Phe Gly Ala Leu Val Ser Gln Lys Pro Arg Arg
10 15 20 25

gac atc tgt caa cgt ggg acc tcc att acc atc cac tgt gag gtc gat 147
Asp Ile Cys Gln Arg Gly Thr Ser Ile Thr Ile His Cys Glu Val Asp
30 35 40

acc caa gtc acc ttg atg ttc tgg tac cgt cag ctc cca gga cag agc 195
Thr Gln Val Thr Leu Met Phe Trp Tyr Arg Gln Leu Pro Gly Gln Ser
45 50 55

ttg ata ctg att gca acc gca aac cag ggt gca gag gcc acc tac gaa 243
Leu Ile Leu Ile Ala Thr Ala Asn Gln Gly Ala Glu Ala Thr Tyr Glu
60 65 70

agt gga ttt acc agg gag aag ttt ccc atc agc cgc cga acc cta atg 291
Ser Gly Phe Thr Arg Glu Lys Phe Pro Ile Ser Arg Arg Thr Leu Met
75 80 85

ttc	tcc	act	ctg	act	gtg	agc	aac	ctg	agc	ctc	gaa	gac	acc	agc	tct	339
Phe	Ser	Thr	Leu	Thr	Val	Ser	Asn	Leu	Ser	Leu	Glu	Asp	Thr	Ser	Ser	
90					95					100					105	

tac ttc tgc agc att tgg tac ggg gag ggg gag cag cac ttt ggg cca 387

Tyr Phe Cys Ser Ile Trp Tyr Gly Glu Gly Glu Gln His Phe Gly Pro
 110 115 120

ggg acc cgg ctc acc gtc cta
 Gly Thr Arg Leu Thr Val Leu
 125

408

<210> 5

<211> 128

<212> PRT

<213> Canis familiaris

<400> 5

Met Leu Thr Cys Leu Leu Leu Leu Leu Gly Gln Gly Ser Val Phe Gly
 1 5 10 15

Ala Leu Val Ser Gln Lys Pro Arg Arg Asp Ile Cys Gln Arg Gly Thr
 20 25 30

Ser Ile Thr Ile His Cys Glu Val Asp Thr Gln Val Thr Leu Met Phe
 35 40 45

Trp Tyr Arg Gln Leu Pro Gly Gln Ser Leu Ile Leu Ile Ala Thr Ala
 50 55 60

Asn Gln Gly Ala Glu Ala Thr Tyr Glu Ser Gly Phe Thr Arg Glu Lys
 65 70 75 80

Phe Pro Ile Ser Arg Arg Thr Leu Met Phe Ser Thr Leu Thr Val Ser
 85 90 95

Asn Leu Ser Leu Glu Asp Thr Ser Ser Tyr Phe Cys Ser Ile Trp Tyr
 100 105 110

Gly Glu Gly Glu Gln His Phe Gly Pro Gly Thr Arg Leu Thr Val Leu
 115 120 125

<210> 6

<211> 408

<212> DNA

<213> Canis familiaris

<400> 6

taggacggtg agccgggtcc ctggcccaaa gtgctgctcc cctccccgt accaaatgct 60

gcagaagtaa gagctggtgt cttcagggt cagggtgctc acagtcagag tggagaacat 120

tagggttcgg cggtgatgg gaaacttctc cctggtaaatt ccactttcgt aggtggcctc 180

tgcaccctgg tttgcggttg caatcagtat caagctctgt cctgggagct gacggtacca 240

gaacatcaag gtgacttggg tatcgacctc acagtggatg gtaatggagg tcccacgttg 300

acagatgtcc ctgcgcggct tttgagagac aagagctcca aacacagagc cttgtcccag 360

gaggagtagc aggcaagtca gcattcttag gtgctagecc ttcaccgt 408

<210> 7

<211> 384

<212> DNA

<213> Canis familiaris

<400> 7

atg	ctg	act	tgc	ctg	cta	ctc	ctc	ctg	gga	caa	ggc	tct	gtg	ttt	gga	48
Met	Leu	Thr	Cys	Leu	Leu	Leu	Leu	Leu	Gly	Gln	Gly	Ser	Val	Phe	Gly	
1				5					10					15		

gct	ctt	gtc	tct	caa	aag	ccg	cgc	agg	gac	atc	tgt	caa	cgt	ggg	acc	96
Ala	Leu	Val	Ser	Gln	Lys	Pro	Arg	Arg	Asp	Ile	Cys	Gln	Arg	Gly	Thr	
			20					25					30			

tcc	att	acc	atc	cac	tgt	gag	gtc	gat	acc	caa	gtc	acc	ttg	atg	ttc	144
Ser	Ile	Thr	Ile	His	Cys	Glu	Val	Asp	Thr	Gln	Val	Thr	Leu	Met	Phe	
			35					40					45			

tgg	tac	cgt	cag	ctc	cca	gga	cag	agc	ttg	ata	ctg	att	gca	acc	gca	192
Trp	Tyr	Arg	Gln	Leu	Pro	Gly	Gln	Ser	Leu	Ile	Leu	Ile	Ala	Thr	Ala	
	50					55					60					

aac	cag	ggt	gca	gag	gcc	acc	tac	gaa	agt	gga	ttt	acc	agg	gag	aag	240
Asn	Gln	Gly	Ala	Glu	Ala	Thr	Tyr	Glu	Ser	Gly	Phe	Thr	Arg	Glu	Lys	
65					70					75				80		

ttt	ccc	atc	agc	cgc	cga	acc	cta	atg	ttc	tcc	act	ctg	act	gtg	agc	288
Phe	Pro	Ile	Ser	Arg	Arg	Thr	Leu	Met	Phe	Ser	Thr	Leu	Thr	Val	Ser	
				85					90					95		

aac	ctg	agc	ctc	gaa	gac	acc	agc	tct	tac	ttc	tgc	agc	att	tgg	tac	336
Asn	Leu	Ser	Leu	Glu	Asp	Thr	Ser	Ser	Tyr	Phe	Cys	Ser	Ile	Trp	Tyr	
			100					105					110			

ggg	gag	ggg	gag	cag	cac	ttt	ggg	cca	ggg	acc	cgg	ctc	acc	gtc	cta	384
Gly	Glu	Gly	Glu	Gln	His	Phe	Gly	Pro	Gly	Thr	Arg	Leu	Thr	Val	Leu	
	115						120					125				

<210> 8

<211> 384

<212> DNA

<213> Canis familiaris

<400> 8

taggacgggtg agccgggtcc ctggcccaaa gtgctgctcc ccctccccgt accaaatgct 60
gcagaagtaa gagctggtgt cttcgaggct caggttgctc acagtcagag tggagaacat 120
tagggttcgg cggctgatgg gaaacttctc cctggtaa at ccactttcgt aggtggcctc 180
tgcaccctgg tttgcggttg caatcagtat caagctctgt cctgggagct gacggtacca 240
gaacatcaag gtgacttggg tatcgacctc acagtggatg gtaatggagg tcccacgttg 300
acagatgtcc ctgcgcggct tttgagagac aagagctcca aacacagagc cttgtcccag 360
gaggagtagc aggcaagtca gcat 384

<210> 9

<211> 408

<212> DNA

<213> Canis familiaris

<220>

<221> CDS

<222> (7)..(408)

<400> 9

gctgaa atg gcc acc ggc gtc ttc ttt ggc atg gct ctt tgt gtc ctg 48
Met Ala Thr Gly Val Phe Phe Gly Met Ala Leu Cys Val Leu
1 5 10

tgg aca gga tac atg gat gct gga att atc cag agc cca aga tac aag 96
Trp Thr Gly Tyr Met Asp Ala Gly Ile Ile Gln Ser Pro Arg Tyr Lys
15 20 25 30

~~gtc aca ggg aca gga aag agg gtg act ctg aga tgt cac cag aca gac 144~~
Val Thr Gly Thr Gly Lys Arg Val Thr Leu Arg Cys His Gln Thr Asp
35 40 45

aac tat gac tat atg tac tgg tat cga cat gac ctg gga cat ggg ccg 192
Asn Tyr Asp Tyr Met Tyr Trp Tyr Arg His Asp Leu Gly His Gly Pro
50 55 60

agg ctg atc tat tat tca aat ggt att aac agc act gaa aaa gga gac 240
Arg Leu Ile Tyr Tyr Ser Asn Gly Ile Asn Ser Thr Glu Lys Gly Asp
65 70 75

ctc tcc aat gga tac aca gtc tct aga tca aac aag atg gat ttc ccc 288
Leu Ser Asn Gly Tyr Thr Val Ser Arg Ser Asn Lys Met Asp Phe Pro
80 85 90

ctc cta ctg gac tct gtt acc tcc tcc cag aca tct gtg tac ttc tgt 336
 Leu Leu Leu Asp Ser Val Thr Ser Ser Gln Thr Ser Val Tyr Phe Cys
 95 100 105 110

gcc gac acg agg gat cct gtt gca gta aat tat gat ttt aac ttt ggc 384
 Ala Asp Thr Arg Asp Pro Val Ala Val Asn Tyr Asp Phe Asn Phe Gly
 115 120 125

cca ggg acc aag ctg aca gtc gta 408
 Pro Gly Thr Lys Leu Thr Val Val
 130

<210> 10

<211> 134

<212> PRT

<213> Canis familiaris

<400> 10

Met Ala Thr Gly Val Phe Phe Gly Met Ala Leu Cys Val Leu Trp Thr
 1 5 10 15

Gly Tyr Met Asp Ala Gly Ile Ile Gln Ser Pro Arg Tyr Lys Val Thr
 20 25 30

Gly Thr Gly Lys Arg Val Thr Leu Arg Cys His Gln Thr Asp Asn Tyr
 35 40 45

Asp Tyr Met Tyr Trp Tyr Arg His Asp Leu Gly His Gly Pro Arg Leu
 50 55 60

Ile Tyr Tyr Ser Asn Gly Ile Asn Ser Thr Glu Lys Gly Asp Leu Ser
 65 70 75 80

Asn Gly Tyr Thr Val Ser Arg Ser Asn Lys Met Asp Phe Pro Leu Leu
 85 90 95

Leu Asp Ser Val Thr Ser Ser Gln Thr Ser Val Tyr Phe Cys Ala Asp
 100 105 110

Thr Arg Asp Pro Val Ala Val Asn Tyr Asp Phe Asn Phe Gly Pro Gly
 115 120 125

Thr Lys Leu Thr Val Val
 130

<210> 11

<211> 408

<212> DNA

<213> Canis familiaris

<400> 11

tacgactgtc agcttggtcc ctgggcaaaa gttaaaatca taatttactg caacaggatc 60
 cctcgtgtcg gcacagaagt acacagatgt ctgggaggag gtaacagagt ccagtaggag 120
 ggggaaatcc atcttgtttg atctagagac tgtgtatcca ttggagaggt ctcctttttc 180
 agtgctgtta ataccatttg aataatagat cagcctcggc ccatgtccca ggtcatgtcg 240
 ataccagtac atatagtcac agttgtctgt ctggtgacat ctcagagtca ccctcttttc 300
 tgtccctgtg accttgatc ttgggtctgt gataattcca gcatccatgt atcctgtcca 360
 caggacacaa agagccatgc caaagaagac gccggtggcc atttcagc 408

<210> 12

<211> 402

<212> DNA

<213> Canis familiaris

<220>

<221> CDS

<222> (1)..(402)

<400> 12

atg gcc acc ggc gtc ttc ttt ggc atg gct ctt tgt gtc ctg tgg aca 48
 Met Ala Thr Gly Val Phe Phe Gly Met Ala Leu Cys Val Leu Trp Thr
 1 5 10 15

gga tac atg gat gct gga att atc cag agc cca aga tac aag gtc aca 96
 Gly Tyr Met Asp Ala Gly Ile Ile Gln Ser Pro Arg Tyr Lys Val Thr
 20 25 30

ggg aca gga aag agg gtg act ctg aga tgt cac cag aca gac aac tat 144
 Gly Thr Gly Lys Arg Val Thr Leu Arg Cys His Gln Thr Asp Asn Tyr
 35 40 45

gac tat atg tac tgg tat cga cat gac ctg gga cat ggg ccg agg ctg 192
 Asp Tyr Met Tyr Trp Tyr Arg His Asp Leu Gly His Gly Pro Arg Leu
 50 55 60

atc tat tat tca aat ggt att aac agc act gaa aaa gga gac ctc tcc 240
 Ile Tyr Tyr Ser Asn Gly Ile Asn Ser Thr Glu Lys Gly Asp Leu Ser
 65 70 75 80

aat gga tac aca gtc tct aga tca aac aag atg gat ttc ccc ctc cta 288
 Asn Gly Tyr Thr Val Ser Arg Ser Asn Lys Met Asp Phe Pro Leu Leu
 85 90 95

ctg gac tct gtt acc tcc tcc cag aca tct gtg tac ttc tgt gcc gac 336
 Leu Asp Ser Val Thr Ser Ser Gln Thr Ser Val Tyr Phe Cys Ala Asp
 100 105 110

acg agg gat cct gtt gca gta aat tat gat ttt aac ttt ggc cca ggg 384
 Thr Arg Asp Pro Val Ala Val Asn Tyr Asp Phe Asn Phe Gly Pro Gly
 115 120 125

acc aag ctg aca gtc gta 402
 Thr Lys Leu Thr Val Val
 130

<210> 13
 <211> 402
 <212> DNA
 <213> Canis familiaris

<400> 13
 tacgactgtc agcttggtcc ctggggccaaa gttaaaatca taatttactg caacaggatc 60
 cctcgtgtcg gcacagaagt acacagatgt ctgggaggag gtaacagagt ccagtaggag 120
 ggggaaatcc atcttgtttg atctagagac tgtgtatcca ttggagaggt ctccctttttc 180
 agtgctgtta ataccatttg aataatagat cagcctcggc ccatgtccca ggtcatgtcg 240
 ataccagtac atatagtcac agttgtctgt ctgggtgacat ctcagagtca ccctcttttcc 300
 tgtccctgtg accttgtatc ttgggctctg gataattcca gcatccatgt atcctgtcca 360
 -----caggacacaa agagecatgc caaagaagac gccggtggcc at----- 402

<210> 14
 <211> 483
 <212> DNA
 <213> Canis familiaris

<220>
 <221> CDS
 <222> (85)..(483)

<400> 14
 aattaaccct cactaaaggg aacaaaagct ggagctccac cgcggcacga ggagcgggga 60
 ggctatcagc ttcccagggc tgcc atg ggc tcc agg ctt ctc tgc tgt gtg 111
 Met Gly Ser Arg Leu Leu Cys Cys Val
 1 5

gcc ctt tgt ctc ctg gga gcc ggc ccc gtg gag tct gag gtc atc caa 159
 Ala Leu Cys Leu Leu Gly Ala Gly Pro Val Glu Ser Glu Val Ile Gln
 10 15 20 25

 act cca aga cac atg atc aaa gca aga gga cag aca gtg acc ctg aga 207
 Thr Pro Arg His Met Ile Lys Ala Arg Gly Gln Thr Val Thr Leu Arg
 30 35 40

 tgt tcc ctt atc tct gga cac cta tct gtg tac tgg tac caa cag gcc 255
 Cys Ser Leu Ile Ser Gly His Leu Ser Val Tyr Trp Tyr Gln Gln Ala
 45 50 55

 ctg ggc cag ggt ccc cgg ttt ctc att cag tat tac aat agg gaa gag 303
 Leu Gly Gln Gly Pro Arg Phe Leu Ile Gln Tyr Tyr Asn Arg Glu Glu
 60 65 70

 aga gac aaa gga gac atc ccg gca aga ttc tca gtg cag cag ttc agt 351
 Arg Asp Lys Gly Asp Ile Pro Ala Arg Phe Ser Val Gln Gln Phe Ser
 75 80 85

 aac tac agc tcc cag ctg gag atg aac tcc ctg gag cca gga gac tca 399
 Asn Tyr Ser Ser Gln Leu Glu Met Asn Ser Leu Glu Pro Gly Asp Ser
 90 95 100 105

 gcc cta tat ctc tgt gcc agc agc tta gat gcg ttc gac gcg ggg cag 447
 Ala Leu Tyr Leu Cys Ala Ser Ser Leu Asp Ala Phe Asp Ala Gly Gln
 110 115 120

 ctg tac ttc ggg gcc ggt tcc aag ctg gcc gtg ctg 483
 Leu Tyr Phe Gly Ala Gly Ser Lys Leu Ala Val Leu
 125 130

<210> 15

<211> 133

<212> PRT

<213> Canis familiaris.

<400> 15

Met Gly Ser Arg Leu Leu Cys Cys Val Ala Leu Cys Leu Leu Gly Ala
 1 5 10 15

Gly Pro Val Glu Ser Glu Val Ile Gln Thr Pro Arg His Met Ile Lys
 20 25 30

Ala Arg Gly Gln Thr Val Thr Leu Arg Cys Ser Leu Ile Ser Gly His
 35 40 45

Leu Ser Val Tyr Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Arg Phe

50 55 60
 Leu Ile Gln Tyr Tyr Asn Arg Glu Glu Arg Asp Lys Gly Asp Ile Pro
 65 70 75 80
 Ala Arg Phe Ser Val Gln Gln Phe Ser Asn Tyr Ser Ser Gln Leu Glu
 85 90 95
 Met Asn Ser Leu Glu Pro Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
 100 105 110
 Ser Leu Asp Ala Phe Asp Ala Gly Gln Leu Tyr Phe Gly Ala Gly Ser
 115 120 125
 Lys Leu Ala Val Leu
 130

<210> 16
 <211> 483
 <212> DNA
 <213> Canis familiaris

<400> 16
 cagcacggcc agcttgaac cggccccgaa gtacagctgc cccgcgtcga acgcatctaa 60
 gctgctggca cagagatata gggctgagtc tcttggtcc agggagtcca tctccagctg 120
 ggagctgtag ttactgaact gctgcactga gaatcttgcc gggatgtctc ctttgtctct 180
 ctcttccta ttgtaatact gaatgagaaa cgggggaccc tggcccaggg cctgttggtta 240
 ccagtacaca gataggtgtc cagagataag ggaacatctc agggtcactg tctgtcctct 300
 tgctttgatc atgtgtcttg gagtttggat gacctcagac tccacggggc cggctcccag 360
 gagacaaagg gccacacagc agagaagcct ggagcccatg gcagccctgg gaagctgata 420
 gcctccccgc tctcgtgcc gcggtggagc tccagctttt gttcccttta gtgagggtta 480
 att 483

<210> 17
 <211> 399
 <212> DNA
 <213> Canis familiaris

<220>
 <221> CDS
 <222> (1)..(399)

<400> 17

atg ggc tcc agg ctt ctc tgc tgt gtg gcc ctt tgt ctc ctg gga gcc 48
 Met Gly Ser Arg Leu Leu Cys Cys Val Ala Leu Cys Leu Leu Gly Ala
 1 5 10 15

ggc ccc gtg gag tct gag gtc atc caa act cca aga cac atg atc aaa 96
 Gly Pro Val Glu Ser Glu Val Ile Gln Thr Pro Arg His Met Ile Lys
 20 25 30

gca aga gga cag aca gtg acc ctg aga tgt tcc ctt atc tct gga cac 144
 Ala Arg Gly Gln Thr Val Thr Leu Arg Cys Ser Leu Ile Ser Gly His
 35 40 45

cta tct gtg tac tgg tac caa cag gcc ctg ggc cag ggt ccc cgg ttt 192
 Leu Ser Val Tyr Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Arg Phe
 50 55 60

ctc att cag tat tac aat agg gaa gag aga gac aaa gga gac atc ccg 240
 Leu Ile Gln Tyr Tyr Asn Arg Glu Glu Arg Asp Lys Gly Asp Ile Pro
 65 70 75 80

gca aga ttc tca gtg cag cag ttc agt aac tac agc tcc cag ctg gag 288
 Ala Arg Phe Ser Val Gln Gln Phe Ser Asn Tyr Ser Ser Gln Leu Glu
 85 90 95

atg aac tcc ctg gag cca gga gac tca gcc cta tat ctc tgt gcc agc 336
 Met Asn Ser Leu Glu Pro Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
 100 105 110

agc tta gat gcg ttc gac gcg ggg cag ctg tac ttc ggg gcc ggt tcc 384
 Ser Leu Asp Ala Phe Asp Ala Gly Gln Leu Tyr Phe Gly Ala Gly Ser
 115 120 125

aag ctg gcc gtg ctg 399
 Lys Leu Ala Val Leu
 130

<210> 18

<211> 399

<212> DNA

<213> Canis familiaris

<400> 18

cagcacggcc agcttggaac cggccccgaa gtacagctgc cccgcgtcga acgcatctaa 60

gctgctggca cagagatata gggctgagtc tcctggctcc agggagttca tctccagctg 120
 ggagctgtag ttactgaact gctgcactga gaatcttgcc gggatgtctc ctttgtctct 180

ctcttccta ttgtaatact gaatgagaaa ccggggaccc tggcccaggg cctgttggtta 240

ccagtacaca gataggtgtc cagagataag ggaacatctc agggtcactg tctgtcctct 300
 tgctttgatc atgtgtcttg gagtttggat gacctcagac tccacggggc cggctcccag 360
 gagacaaagg gccacacagc agagaagcct ggagcccat 399

<210> 19

<211> 462

<212> DNA

<213> Canis familiaris

<220>

<221> CDS

<222> (73)..(462)

<400> 19

gctgcaggat tcggcacgag gcgtgggtcat atctatcttg agagaggtat ggtatgaggc 60

catcacctga ag atg ctg atg ctt ctg ctg ctc ctg ggg ccc agc tct gga 111
 Met Leu Met Leu Leu Leu Leu Leu Gly Pro Ser Ser Gly
 1 5 10

ctc ggt gcc ctc gtc ttc cag gcg ccc agc aca atg atc tgt aag agc 159
 Leu Gly Ala Leu Val Phe Gln Ala Pro Ser Thr Met Ile Cys Lys Ser
 15 20 25

gga gcc acc gtg cag atc cag tgt caa aca gtg gac ctt caa gcc aca 207
 Gly Ala Thr Val Gln Ile Gln Cys Gln Thr Val Asp Leu Gln Ala Thr
 30 35 40 45

acc gtg ttt tgg tat cgc cag ctc ccg aag cag ggc ctt acc ctt atg 255
 Thr Val Phe Trp Tyr Arg Gln Leu Pro Lys Gln Gly Leu Thr Leu Met
 50 55 60

gtg acc tct aac gtg ggc aac agt gct aca cac gag cag ggg ttc cct 303
 Val Thr Ser Asn Val Gly Asn Ser Ala Thr His Glu Gln Gly Phe Pro
 65 70 75

gca gcc aag ttc cct gtt aac cac cca aac ctc acg ttt tcc tcc ctg 351
 Ala Ala Lys Phe Pro Val Asn His Pro Asn Leu Thr Phe Ser Ser Leu
 80 85 90

atg gtg acg agt tca ggt cct gga gac agc ggc ctc tac ttc tgt ggt 399
 Met Val Thr Ser Ser Gly Pro Gly Asp Ser Gly Leu Tyr Phe Cys Gly
 95 100 105

gtt cgg gcg tat ggt ggg aac tcg ccc ctc tac ttt gga aca ggc acc 447
 Val Arg Ala Tyr Gly Gly Asn Ser Pro Leu Tyr Phe Gly Thr Gly Thr
 110 115 120 125

agg ctc acc gtg aca
Arg Leu Thr Val Thr
130

462

<210> 20
<211> 130
<212> PRT
<213> Canis familiaris

<400> 20
Met Leu Met Leu Leu Leu Leu Gly Pro Ser Ser Gly Leu Gly Ala
1 5 10 15
Leu Val Phe Gln Ala Pro Ser Thr Met Ile Cys Lys Ser Gly Ala Thr
20 25 30
Val Gln Ile Gln Cys Gln Thr Val Asp Leu Gln Ala Thr Thr Val Phe
35 40 45
Trp Tyr Arg Gln Leu Pro Lys Gln Gly Leu Thr Leu Met Val Thr Ser
50 55 60
Asn Val Gly Asn Ser Ala Thr His Glu Gln Gly Phe Pro Ala Ala Lys
65 70 75 80
Phe Pro Val Asn His Pro Asn Leu Thr Phe Ser Ser Leu Met Val Thr
85 90 95
Ser Ser Gly Pro Gly Asp Ser Gly Leu Tyr Phe Cys Gly Val Arg Ala
100 105 110
Tyr Gly Gly Asn Ser Pro Leu Tyr Phe Gly Thr Gly Thr Arg Leu Thr
115 120 125
Val Thr
130

<210> 21
<211> 462
<212> DNA
<213> Canis familiaris

<400> 21
tgtcacggtg agcctggtgc ctgttccaaa gtagaggggc gagttccac catagcccg 60
aacaccacag aagtagagge cgctgtctcc aggacctgaa ctcgtcacca tcaggaggga 120

aaacgtgagg tttgggtggt taacagggaa cttggctgca gggaaccctt gctcgtgtgt 180
 agcactgttg ccacagttag aggtcaccat aagggttaagg ccctgcttcg ggagctggcg 240
 ataccaaaac acggttgtgg cttgaaggtc cactgtttga cactggatct gcacggtggc 300
 tccgctctta cagatcattg tgctgggcgc ctggaagacg agggcaccga gtccagagct 360
 gggccccagg agcagcagaa gcatcagcat cttcaggtga tggcctcata ccatacctct 420
 ctcaagatag atatgaccac gcctcgtgcc gaatcctgca gc 462

<210> 22
 <211> 417
 <212> DNA
 <213> Canis familiaris
 <220>
 <221> CDS
 <222> (13)..(417)

<400> 22
 cagcagcctg cc atg tgc cca gtg ttc atc tgc tcc ttg gtc ctc tgg ctc 51
 Met Cys Pro Val Phe Ile Cys Ser Leu Val Leu Trp Leu
 1 5 10
 ctg agt aca ggc acc ctc aat gca aaa gtc atg cag act cca gga cat 99
 Leu Ser Thr Gly Thr Leu Asn Ala Lys Val Met Gln Thr Pro Gly His
 15 20 25
 ctg gtc aaa ggg aaa gga caa aaa gca aaa atg gaa tgt gtc cca ata 147
 Leu Val Lys Gly Lys Gly Gln Lys Ala Lys Met Glu Cys Val Pro Ile
 30 35 40 45

aaa gga cat agt tat gtt ttc tgg tat cag cag atc cca gca aaa gag 195
 Lys Gly His Ser Tyr Val Phe Trp Tyr Gln Gln Ile Pro Ala Lys Glu
 50 55 60
 ttc aag ttc ttg att tct ttc cag gat aac gct gtc ttt gat aaa aca 243
 Phe Lys Phe Leu Ile Ser Phe Gln Asp Asn Ala Val Phe Asp Lys Thr
 65 70 75
 ggg atg ccc acg cag aga ttt tta gcc ttg tgt cca aaa aac cta ccc 291
 Gly Met Pro Thr Gln Arg Phe Leu Ala Leu Cys Pro Lys Asn Leu Pro
 80 85 90
 tgt agc cta gag atc gag cgt aca gag ctg cag gat tca gcc gtg tat 339
 Cys Ser Leu Glu Ile Glu Arg Thr Glu Leu Gln Asp Ser Ala Val Tyr
 95 100 105
 ttt tgt gcc agc agt gac aga act ggg gga ctc gtt cac gag cag tat 387

Phe Cys Ala Ser Ser Asp Arg Thr Gly Gly Leu Val His Glu Gln Tyr
 110 115 120 125

ttc ggc gcc ggc acc agg ctc acg gtc ctc 417
 Phe Gly Ala Gly Thr Arg Leu Thr Val Leu
 130 135

<210> 23
 <211> 135
 <212> PRT
 <213> Canis familiaris

<400> 23
 Met Cys Pro Val Phe Ile Cys Ser Leu Val Leu Trp Leu Leu Ser Thr
 1 5 10 15

Gly Thr Leu Asn Ala Lys Val Met Gln Thr Pro Gly His Leu Val Lys
 20 25 30

Gly Lys Gly Gln Lys Ala Lys Met Glu Cys Val Pro Ile Lys Gly His
 35 40 45

Ser Tyr Val Phe Trp Tyr Gln Gln Ile Pro Ala Lys Glu Phe Lys Phe
 50 55 60

Leu Ile Ser Phe Gln Asp Asn Ala Val Phe Asp Lys Thr Gly Met Pro
 65 70 75 80

Thr Gln Arg Phe Leu Ala Leu Cys Pro Lys Asn Leu Pro Cys Ser Leu
 85 90 95

~~Glu Ile Glu Arg Thr Glu Leu Gln Asp Ser Ala Val Tyr Phe Cys Ala~~
 100 105 110

Ser Ser Asp Arg Thr Gly Gly Leu Val His Glu Gln Tyr Phe Gly Ala
 115 120 125

Gly Thr Arg Leu Thr Val Leu
 130 135

<210> 24
 <211> 417
 <212> DNA
 <213> Canis familiaris

<400> 24
 gaggaccgtg agcctggtgc cggcgccgaa atactgctcg tgaacgagtc cccagttct 60

[illegible]

tct gct gtg tat ttc tgt gcc agc agc gag ggg tat gat gaa aaa ttg 390
 Ser Ala Val Tyr Phe Cys Ala Ser Ser Glu Gly Tyr Asp Glu Lys Leu
 105 110 115

tat ttt gca agt gga acc aag ctt tct gtc ttg 423
 Tyr Phe Ala Ser Gly Thr Lys Leu Ser Val Leu
 120 125

<210> 26

<211> 128

<212> PRT

<213> Canis familiaris

<400> 26

Met Gly Ser Gly Phe Leu Cys Cys Met Val Leu Cys Leu Leu Gly Ala
 1 5 10 15

Ala Pro Leu Asp Thr Thr Val Ser Gln Thr Pro Arg Tyr Leu Ile Ala
 20 25 30

His Val Gly Ser Lys Lys Leu Leu Lys Cys Glu Gln Asn Leu Gly His
 35 40 45

Asn Ala Met Tyr Trp Tyr Lys Gln Asp Leu Lys Gln Leu Leu Lys Ile
 50 55 60

Met Phe Ile Tyr Phe Asn Gln Gly Leu Asn Leu Asn Glu Ser Val Pro
 65 70 75 80

Gly Arg Phe Ser Pro Glu Thr Leu Thr Ser Ser Leu Thr Ser Cys Arg
 85 90 95

~~Leu Leu Asn Ser Asp Ser Ala Val Tyr Phe Cys Ala Ser Ser Glu Gly~~
 100 105 110

Tyr Asp Glu Lys Leu Tyr Phe Ala Ser Gly Thr Lys Leu Ser Val Leu
 115 120 125

<210> 27

<211> 423

<212> DNA

<213> Canis familiaris

<400> 27

caagacagaa agcttggttc cacttgcaaa atacaatttt tcatcatacc cctcgctgct 60

ggcacagaaa tacacagcag agtcactgtt caggagtoga catgaagtta atgagcttgt 120

cagtgtctca ggtgagaaac gacctggaac tgattcattt agattgagtc cctgattaaa 180

gtagataaac atgatcttca gcagttgctt gaggtcttgc ttataccagt acatagcatt 240
 atggcccaga ttttgtcac attttagtaa cttcttcgat cccacgtgcg cgatgaggta 300
 tcttggagtc tgggaaactg ttgtgtccag ggggtgctgt cccaggaggc agaggacat 360
 acagcagagg aaccgggagc ccatggtgga gacaggcaca gtctggtcct cagtgtcgt 420
 gcc 423

<210> 28
 <211> 333
 <212> DNA
 <213> Canis familiaris

<220>
 <221> CDS
 <222> (1)..(333)

<400> 28
 atc gga ctc ctc tgt ggt gtg gcc ttt tgt ttc ctg gga gta ggc ctt 48
 Ile Gly Leu Leu Cys Gly Val Ala Phe Cys Phe Leu Gly Val Gly Leu
 1 5 10 15
 ttg aac gca caa gtg act caa acc ccg aga caa ctc atc aaa aaa gtg 96
 Leu Asn Ala Gln Val Thr Gln Thr Pro Arg Gln Leu Ile Lys Lys Val
 20 25 30
 gga gcg aaa gtt ttg ttg aaa tgt tca cag aat atg gac cat gaa aga 144
 Gly Ala Lys Val Leu Leu Lys Cys Ser Gln Asn Met Asp His Glu Arg
 35 40 45

atg ttc tgg tat cga caa gac cca ggt ctg ggg ttg cgg ctg ctc tac 192
 Met Phe Trp Tyr Arg Gln Asp Pro Gly Leu Gly Leu Arg Leu Leu Tyr
 50 55 60
 tgg tcc tat aat att gac agt gtt gag aca gga gac atc cct tat ggg 240
 Trp Ser Tyr Asn Ile Asp Ser Val Glu Thr Gly Asp Ile Pro Tyr Gly
 65 70 75 80
 tac agt gtc tcg agg aag aag aag gat gcc ttc ccc ttg att ctg gag 288
 Tyr Ser Val Ser Arg Lys Lys Lys Asp Ala Phe Pro Leu Ile Leu Glu
 85 90 95
 tct gct cgc atc aac cag aca tct gtg tac ttc tgc gcc agc agc 333
 Ser Ala Arg Ile Asn Gln Thr Ser Val Tyr Phe Cys Ala Ser Ser
 100 105 110

<210> 29

<211> 111

<212> PRT

<213> Canis familiaris

<400> 29

Ile Gly Leu Leu Cys Gly Val Ala Phe Cys Phe Leu Gly Val Gly Leu
 1 5 10 15

Leu Asn Ala Gln Val Thr Gln Thr Pro Arg Gln Leu Ile Lys Lys Val
 20 25 30

Gly Ala Lys Val Leu Leu Lys Cys Ser Gln Asn Met Asp His Glu Arg
 35 40 45

Met Phe Trp Tyr Arg Gln Asp Pro Gly Leu Gly Leu Arg Leu Leu Tyr
 50 55 60

Trp Ser Tyr Asn Ile Asp Ser Val Glu Thr Gly Asp Ile Pro Tyr Gly
 65 70 75 80

Tyr Ser Val Ser Arg Lys Lys Lys Asp Ala Phe Pro Leu Ile Leu Glu
 85 90 95

Ser Ala Arg Ile Asn Gln Thr Ser Val Tyr Phe Cys Ala Ser Ser
 100 105 110

<210> 30

<211> 333

<212> DNA

<213> Canis familiaris

<400> 30

~~gctactggeg cagaagtaca cagatgtctg gttgatgega gcagactcca gaatcaaggg~~ 60

gaaggcatcc ttcttcttcc tcgagacact gtacccataa gggatgtctc ctgtctcaac 120

actgtcaata ttataggacc agtagagcag ccgcaacccc agacctgggt cttgtcgata 180

ccagaacatt ctttcattgt ccatattctg tgaacatttc aacaaaactt tcgctccac 240

ttttttgatg agttgtctcg gggtttgagt cacttgtgcg ttcaaaaggc ctactcccag 300

gaaacaaaag gccacaccac agaggagtcc gat 333

<210> 31

<211> 351

<212> DNA

<213> Canis familiaris

<220>

<221> CDS

<222> (25)..(351)

<400> 31

acggtgaagg gctagcacct aaag atg ctg act tgc ctg cta ctc ctc ctg 51
 Met Leu Thr Cys Leu Leu Leu Leu Leu

1

5

gga caa ggc tct gtg ttt gga gct ctt gtc tct caa aag ccg cgc agg 99
 Gly Gln Gly Ser Val Phe Gly Ala Leu Val Ser Gln Lys Pro Arg Arg
 10 15 20 25

gac atc tgt caa cgt ggg acc tcc att acc atc cac tgt gag gtc gat 147
 Asp Ile Cys Gln Arg Gly Thr Ser Ile Thr Ile His Cys Glu Val Asp
 30 35 40

acc caa gtc acc ttg atg ttc tgg tac cgt cag ctc cca gga cag agc 195
 Thr Gln Val Thr Leu Met Phe Trp Tyr Arg Gln Leu Pro Gly Gln Ser
 45 50 55

ttg ata ctg att gca acc gca aac cag ggt gca gag gcc acc tac gaa 243
 Leu Ile Leu Ile Ala Thr Ala Asn Gln Gly Ala Glu Ala Thr Tyr Glu
 60 65 70

agt gga ttt acc agg gag aag ttt ccc atc agc cgc cga acc cta atg 291
 Ser Gly Phe Thr Arg Glu Lys Phe Pro Ile Ser Arg Arg Thr Leu Met
 75 80 85

ttc tcc act ctg act gtg agc aac ctg agc ctc gaa gac acc agc tct 339
 Phe Ser Thr Leu Thr Val Ser Asn Leu Ser Leu Glu Asp Thr Ser Ser
 90 95 100 105

tac ttc tgc agc 351
 Tyr Phe Cys Ser

<210> 32

<211> 109

<212> PRT

<213> Canis familiaris

<400> 32

Met Leu Thr Cys Leu Leu Leu Leu Leu Gly Gln Gly Ser Val Phe Gly
 1 5 10 15

Ala Leu Val Ser Gln Lys Pro Arg Arg Asp Ile Cys Gln Arg Gly Thr
 20 25 30

Ser Ile Thr Ile His Cys Glu Val Asp Thr Gln Val Thr Leu Met Phe

35 40 45
 Trp Tyr Arg Gln Leu Pro Gly Gln Ser Leu Ile Leu Ile Ala Thr Ala
 50 55 60
 Asn Gln Gly Ala Glu Ala Thr Tyr Glu Ser Gly Phe Thr Arg Glu Lys
 65 70 75 80
 Phe Pro Ile Ser Arg Arg Thr Leu Met Phe Ser Thr Leu Thr Val Ser
 85 90 95
 Asn Leu Ser Leu Glu Asp Thr Ser Ser Tyr Phe Cys Ser
 100 105

<210> 33
 <211> 351
 <212> DNA
 <213> Canis familiaris

<400> 33
 gctgcagaag taagagctgg tgtcttcgag gctcaggttg ctcacagtca gaggaggagaa 60
 cattaggggtt cggcggtga tgggaaactt ctccctggta aatccacttt cgtaggtggc 120
 ctctgcaccc ttggtttgagg ttgcaatcag tatcaagctc tgtcctggga gctgacggta 180
 ccagaacatc aaggtgactt gggatatcag ctcacagtgg atggtaatgg aggtcccacg 240
 ttgacagatg tccctgcgag gctttttgaga gacaagagct ccaaacacag agccttgtcc 300
 caggaggagt agcaggcaag tcagcatctt taggtgctag ccttcaccg t 351

 <210> 34
 <211> 339
 <212> DNA
 <213> Canis familiaris

<220>
 <221> CDS
 <222> (7)..(339)

<400> 34
 gctgaa atg gcc acc ggc gtc ttc ttt ggc atg gct ctt tgt gtc ctg 48
 Met Ala Thr Gly Val Phe Phe Gly Met Ala Leu Cys Val Leu
 1 5 10
 tgg aca gga tac atg gat gct gga att atc cag agc cca aga tac aag 96
 Trp Thr Gly Tyr Met Asp Ala Gly Ile Ile Gln Ser Pro Arg Tyr Lys
 15 20 25 30

gtc aca ggg aca gga aag agg gtg act ctg aga tgt cac cag aca gac 144
 Val Thr Gly Thr Gly Lys Arg Val Thr Leu Arg Cys His Gln Thr Asp
 35 40 45

 aac tat gac tat atg tac tgg tat cga cat gac ctg gga cat ggg ccg 192
 Asn Tyr Asp Tyr Met Tyr Trp Tyr Arg His Asp Leu Gly His Gly Pro
 50 55 60

 agg ctg atc tat tat tca aat ggt att aac agc act gaa aaa gga gac 240
 Arg Leu Ile Tyr Tyr Ser Asn Gly Ile Asn Ser Thr Glu Lys Gly Asp
 65 70 75

 ctc tcc aat gga tac aca gtc tct aga tca aac aag atg gat ttc ccc 288
 Leu Ser Asn Gly Tyr Thr Val Ser Arg Ser Asn Lys Met Asp Phe Pro
 80 85 90

 ctc cta ctg gac tct gtt acc tcc tcc cag aca tct gtg tac ttc tgt 336
 Leu Leu Leu Asp Ser Val Thr Ser Ser Gln Thr Ser Val Tyr Phe Cys
 95 100 105 110

 gcc 339
 Ala

<210> 35

<211> 111

<212> PRT

<213> Canis familiaris

<400> 35

Met Ala Thr Gly Val Phe Phe Gly Met Ala Leu Cys Val Leu Trp Thr
 1 5 10 15

Gly Tyr Met Asp Ala Gly Ile Ile Gln Ser Pro Arg Tyr Lys Val Thr
 20 25 30

Gly Thr Gly Lys Arg Val Thr Leu Arg Cys His Gln Thr Asp Asn Tyr
 35 40 45

Asp Tyr Met Tyr Trp Tyr Arg His Asp Leu Gly His Gly Pro Arg Leu
 50 55 60

Ile Tyr Tyr Ser Asn Gly Ile Asn Ser Thr Glu Lys Gly Asp Leu Ser
 65 70 75 80

Asn Gly Tyr Thr Val Ser Arg Ser Asn Lys Met Asp Phe Pro Leu Leu
 85 90 95

Leu Asp Ser Val Thr Ser Ser Gln Thr Ser Val Tyr Phe Cys Ala
 100 105 110

<210> 36
 <211> 339
 <212> DNA
 <213> Canis familiaris

<400> 36
 ggcacagaag tacacagatg tctgggagga ggtaacagag tccagtagga gggggaaatc 60
 catcttggtt gatctagaga ctgtgtatcc attggagagg tctccttttt cagtgtgtt 120
 aataccattt gaataataga tcagcctcgg cccatgtccc aggtcatgtc gataccagta 180
 catatagtca tagttgtctg tctggtgaca tctcagagtc accctctttc ctgtccctgt 240
 gaccttgtat cttgggctct ggataattcc agcatccatg tatcctgtcc acaggacaca 300
 aagagccatg ccaaagaaga cgccggtggc catttcagc 339

<210> 37
 <211> 423
 <212> DNA
 <213> Canis familiaris

<220>
 <221> CDS
 <222> (85)..(423)

<400> 37
 aattaaccct cactaaaggg aacaaaagct ggagctccac cgccggcacga ggagcgggga 60

ggctatcagc ttcccagggc tgcc atg ggc tcc agg ctt ctc tgc tgt gtg 111
 Met Gly Ser Arg Leu Leu Cys Cys Val
 1 5

gcc ctt tgt ctc ctg gga gcc ggc ccc gtg gag tct gag gtc atc caa 159
 Ala Leu Cys Leu Leu Gly Ala Gly Pro Val Glu Ser Glu Val Ile Gln
 10 15 20 25

act cca aga cac atg atc aaa gca aga gga cag aca gtg acc ctg aga 207
 Thr Pro Arg His Met Ile Lys Ala Arg Gly Gln Thr Val Thr Leu Arg
 30 35 40

tgt tcc ctt atc tct gga cac cta tct gtg tac tgg tac caa cag gcc 255
 Cys Ser Leu Ile Ser Gly His Leu Ser Val Tyr Trp Tyr Gln Gln Ala
 45 50 55

ctg ggc cag ggt ccc cgg ttt ctc att cag tat tac aat agg gaa gag 303
 Leu Gly Gln Gly Pro Arg Phe Leu Ile Gln Tyr Tyr Asn Arg Glu Glu
 60 65 70

aga gac aaa gga gac atc ccg gca aga ttc tca gtg cag cag ttc agt 351
 Arg Asp Lys Gly Asp Ile Pro Ala Arg Phe Ser Val Gln Gln Phe Ser
 75 80 85

aac tac agc tcc cag ctg gag atg aac tcc ctg gag cca gga gac tca 399
 Asn Tyr Ser Ser Gln Leu Glu Met Asn Ser Leu Glu Pro Gly Asp Ser
 90 95 100 105

gcc cta tat ctc tgt gcc agc agc 423
 Ala Leu Tyr Leu Cys Ala Ser Ser
 110

<210> 38
 <211> 113
 <212> PRT
 <213> Canis familiaris

<400> 38
 Met Gly Ser Arg Leu Leu Cys Cys Val Ala Leu Cys Leu Leu Gly Ala
 1 5 10 15

Gly Pro Val Glu Ser Glu Val Ile Gln Thr Pro Arg His Met Ile Lys
 20 25 30

Ala Arg Gly Gln Thr Val Thr Leu Arg Cys Ser Leu Ile Ser Gly His
 35 40 45

Leu Ser Val Tyr Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Arg Phe
 50 55 60

Leu Ile Gln Tyr Tyr Asn Arg Glu Glu Arg Asp Lys Gly Asp Ile Pro
 65 70 75 80

Ala Arg Phe Ser Val Gln Gln Phe Ser Asn Tyr Ser Ser Gln Leu Glu
 85 90 95

Met Asn Ser Leu Glu Pro Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
 100 105 110

Ser

<210> 39
 <211> 423
 <212> DNA
 <213> Canis familiaris

<400> 39
 gctgctggca cagagatata gggctgagtc tcctggctcc agggagttca tctccagctg 60

ggagctgtag ttactgaact gctgcactga gaatcttgcc gggatgtctc ctttgtctct 120
 ctcttcctta ttgtaatact gaatgagaaa ccggggaccc tggcccaggg cctgttggtta 180
 ccagtaacaca gataggtgtc cagagataag ggaacatctc agggtcactg tctgtcctct 240
 tgctttgatc atgtgtcttg gagtttggat gacctcagac tccacggggc cggctcccag 300
 gagacaaagg gccacacagc agagaagcct ggagcccatg gcagccctgg gaagctgata 360
 gcctccccgc tctcgtgcc gcggtggagc tccagctttt gttcccttta gtgagggtta 420
 att 423

<210> 40
 <211> 396
 <212> DNA
 <213> Canis familiaris

<220>
 <221> CDS
 <222> (73)..(396)

<400> 40
 gctgcaggat tccggcacgag gcgtgggtcat atctatcttg agagaggtat ggtatgaggc 60
 catcacctga ag atg ctg atg ctt ctg ctg ctc ctg ggg ccc agc tct gga 111
 Met Leu Met Leu Leu Leu Leu Leu Gly Pro Ser Ser Gly
 1 5 10

ctc ggt gcc ctc gtc ttc cag gcg ccc agc aca atg atc tgt aag agc 159
 Leu Gly Ala Leu Val Phe Gln Ala Pro Ser Thr Met Ile Cys Lys Ser
 15 20 25

gga gcc acc gtg cag atc cag tgt caa aca gtg gac ctt caa gcc aca 207
 Gly Ala Thr Val Gln Ile Gln Cys Gln Thr Val Asp Leu Gln Ala Thr
 30 35 40 45

acc gtg ttt tgg tat cgc cag ctc ccg aag cag ggc ctt acc ctt atg 255
 Thr Val Phe Trp Tyr Arg Gln Leu Pro Lys Gln Gly Leu Thr Leu Met
 50 55 60

gtg acc tct aac gtg ggc aac agt gct aca cac gag cag ggg ttc cct 303
 Val Thr Ser Asn Val Gly Asn Ser Ala Thr His Glu Gln Gly Phe Pro
 65 70 75

gca gcc aag ttc cct gtt aac cac cca aac ctc acg ttt tcc tcc ctg 351
 Ala Ala Lys Phe Pro Val Asn His Pro Asn Leu Thr Phe Ser Ser Leu
 80 85 90

atg gtg acg agt tca ggt cct gga gac agc ggc ctc tac ttc tgt 396
 Met Val Thr Ser Ser Gly Pro Gly Asp Ser Gly Leu Tyr Phe Cys
 95 100 105

<210> 41
 <211> 108
 <212> PRT
 <213> Canis familiaris

<400> 41
 Met Leu Met Leu Leu Leu Leu Gly Pro Ser Ser Gly Leu Gly Ala
 1 5 10 15
 Leu Val Phe Gln Ala Pro Ser Thr Met Ile Cys Lys Ser Gly Ala Thr
 20 25 30
 Val Gln Ile Gln Cys Gln Thr Val Asp Leu Gln Ala Thr Thr Val Phe
 35 40 45
 Trp Tyr Arg Gln Leu Pro Lys Gln Gly Leu Thr Leu Met Val Thr Ser
 50 55 60
 Asn Val Gly Asn Ser Ala Thr His Glu Gln Gly Phe Pro Ala Ala Lys
 65 70 75 80
 Phe Pro Val Asn His Pro Asn Leu Thr Phe Ser Ser Leu Met Val Thr
 85 90 95
 Ser Ser Gly Pro Gly Asp Ser Gly Leu Tyr Phe Cys
 100 105

<210> 42
 <211> 396
 <212> DNA
 <213> Canis familiaris

<400> 42
 acagaagtag aggccgctgt ctccaggacc tgaactcgtc accatcaggg aggaaaacgt 60
 gaggtttggg tgggtaacag ggaacttggc tgcagggaa cctgtctcgt gtgtagcact 120
 gttgcccacg ttagaggtca ccataagggt aaggccctgc ttcgggagct ggcgatacca 180
 aaacacgggt gtggcttgaa ggtccactgt ttgacactgg atctgcacgg tggctccgct 240
 cttacagatc attgtgctgg gcgcctggaa gacgagggca ccgagtccag agctggggccc 300
 caggagcagc agaagcatca gcattctcag gtgatggcct cataccatac ctctctcaag 360

atagatatga ccacgcctcg tgccgaatcc tgcagc

396

<210> 43
 <211> 354
 <212> DNA
 <213> Canis familiaris

<220>
 <221> CDS
 <222> (13)..(354)

<400> 43
 cacgagcctg cc atg tgc cca gtg ttc atc tgc tcc ttg gtc ctc tgg ctc 51
 Met Cys Pro Val Phe Ile Cys Ser Leu Val Leu Trp Leu
 1 5 10

ctg agt aca ggc acc ctc aat gca aaa gtc atg cag act cca gga cat 99
 Leu Ser Thr Gly Thr Leu Asn Ala Lys Val Met Gln Thr Pro Gly His
 15 20 25
 ctg gtc aaa ggg aaa gga caa aaa gca aaa atg gaa tgt gtc cca ata 147
 Leu Val Lys Gly Lys Gly Gln Lys Ala Lys Met Glu Cys Val Pro Ile
 30 35 40 45

aaa gga cat agt tat gtt ttc tgg tat cag cag atc cca gca aaa gag 195
 Lys Gly His Ser Tyr Val Phe Trp Tyr Gln Gln Ile Pro Ala Lys Glu
 50 55 60

ttc aag ttc ttg att tct ttc cag gat aac gct gtc ttt gat aaa aca 243
 Phe Lys Phe Leu Ile Ser Phe Gln Asp Asn Ala Val Phe Asp Lys Thr
 65 70 75

ggg atg ccc acg cag aga ttt tta gcc ttg tgt cca aaa aac cta ccc 291
 Gly Met Pro Thr Gln Arg Phe Leu Ala Leu Cys Pro Lys Asn Leu Pro
 80 85 90

tgt agc cta gag atc gag cgt aca gag ctg cag gat tca gcc gtg tat 339
 Cys Ser Leu Glu Ile Glu Arg Thr Glu Leu Gln Asp Ser Ala Val Tyr
 95 100 105

ttt tgt gcc agc agt 354
 Phe Cys Ala Ser Ser
 110

<210> 44
 <211> 114
 <212> PRT
 <213> Canis familiaris

<400> 44

Met Cys Pro Val Phe Ile Cys Ser Leu Val Leu Trp Leu Leu Ser Thr
 1 5 10 15

Gly Thr Leu Asn Ala Lys Val Met Gln Thr Pro Gly His Leu Val Lys
 20 25 30

Gly Lys Gly Gln Lys Ala Lys Met Glu Cys Val Pro Ile Lys Gly His
 35 40 45

Ser Tyr Val Phe Trp Tyr Gln Gln Ile Pro Ala Lys Glu Phe Lys Phe
 50 55 60

Leu Ile Ser Phe Gln Asp Asn Ala Val Phe Asp Lys Thr Gly Met Pro
 65 70 75 80

Thr Gln Arg Phe Leu Ala Leu Cys Pro Lys Asn Leu Pro Cys Ser Leu
 85 90 95

Glu Ile Glu Arg Thr Glu Leu Gln Asp Ser Ala Val Tyr Phe Cys Ala
 100 105 110

Ser Ser

<210> 45

<211> 354

<212> DNA

<213> Canis familiaris

<400> 45

actgctggca caaaaatata cggctgaatc ctgcagctct gtacgctcga tctctaggct 60

acagggtagg ttttttggac acaaggctaa aaatctctgc gtgggcatcc ctgttttatt 120

aaagacagcg ttatcctgga aagaaatcaa gaacttgaac tcttttgctg ggatctgctg 180

ataccagaaa acataactat gtccttttat tgggacacat tccatttttg ctttttgtcc 240

tttccctttg accagatgtc ctggagtctg catgactttt gcattgaggg tgccgtgtact 300

caggagccag aggaccaagg agcagatgaa cactgggcac atggcaggct cgtg 354

<210> 46

<211> 369

<212> DNA

<213> Canis familiaris

<220>

<221> CDS

<222> (40)..(369)

<400> 46

```

ggcagcagca ctgaggacca gactgtgcct gtctccacc atg ggc tcc ggg ttc      54
                                   Met Gly Ser Gly Phe
                                   1           5

ctc tgc tgt atg gtc ctc tgc ctc ctg gga gca gca ccc ctg gac aca      102
Leu Cys Cys Met Val Leu Cys Leu Leu Gly Ala Ala Pro Leu Asp Thr
               10               15               20

aca gtt tcc cag act cca aga tac ctc atc gcg cac gtg gga tgc aag      150
Thr Val Ser Gln Thr Pro Arg Tyr Leu Ile Ala His Val Gly Ser Lys
               25               30               35

aag tta cta aaa tgt gag caa aat ctg ggc cat aat gct atg tac tgg      198
Lys Leu Leu Lys Cys Glu Gln Asn Leu Gly His Asn Ala Met Tyr Trp
               40               45               50

tat aag caa gac ctc aag caa ctg ctg aag atc atg ttt atc tac ttt      246
Tyr Lys Gln Asp Leu Lys Gln Leu Leu Lys Ile Met Phe Ile Tyr Phe
               55               60               65

aat cag gga ctc aat cta aat gaa tca gtt cca ggt cgt ttc tca cct      294
Asn Gln Gly Leu Asn Leu Asn Glu Ser Val Pro Gly Arg Phe Ser Pro
               70               75               80               85

gag aca ctg aca agc tca tta act tca tgt cga ctc ctg aac agt gac      342
Glu Thr Leu Thr Ser Ser Leu Thr Ser Cys Arg Leu Leu Asn Ser Asp
               90               95               100

tct gct gtg tat ttc tgt gcc agc agc      369
Ser Ala Val Tyr Phe Cys Ala Ser Ser
               105               110

```

<210> 47

<211> 110

<212> PRT

<213> Canis familiaris

<400> 47

```

Met Gly Ser Gly Phe Leu Cys Cys Met Val Leu Cys Leu Leu Gly Ala
 1           5           10           15

Ala Pro Leu Asp Thr Thr Val Ser Gln Thr Pro Arg Tyr Leu Ile Ala
 20           25           30

His Val Gly Ser Lys Lys Leu Leu Lys Cys Glu Gln Asn Leu Gly His
 35           40           45

```

Asn Ala Met Tyr Trp Tyr Lys Gln Asp Leu Lys Gln Leu Leu Lys Ile
 50 55 60
 Met Phe Ile Tyr Phe Asn Gln Gly Leu Asn Leu Asn Glu Ser Val Pro
 65 70 75 80
 Gly Arg Phe Ser Pro Glu Thr Leu Thr Ser Ser Leu Thr Ser Cys Arg
 85 90 95
 Leu Leu Asn Ser Asp Ser Ala Val Tyr Phe Cys Ala Ser Ser
 100 105 110

<210> 48
 <211> 369
 <212> DNA
 <213> Canis familiaris

<400> 48
 gctgctggca cagaaatata cagcagagtc actgttcagg agtcgacatg aagttaatga 60
 gcttgctcagt gtctcaggtg agaaacgacc tggaactgat tcatttagat tgagtcacctg 120
 attaaagtag ataaacatga tcttcagcag ttgcttgagg tcttgcttat accagtacat 180
 agcattatgg ccagatattt gtcacattt tagtaacttc ttgatccca cgtgcgcgat 240
 gaggtatctt ggagtctggg aaactgttgt gtccaggggt gctgctccca ggaggcagag 300
 gaccatacag cagaggaacc cggagcccat ggtggagaca ggcacagtct ggtcctcagt 360
 gctcgtgcc 369

<210> 49
 <211> 504
 <212> DNA
 <213> Canis familiaris

<400> 49
 gaggatctgc agaaggtcac ccctcccacg gtcacagtgt ttgaaccatc ggaagcagag 60
 atctcgcgga ccagaaggc cacactcgtg tgcttgccca cgggcttcta ccccgaccac 120
 gtggagctga gctgggtgggt gaacgggaag gaggtcacga gtgggttcag caccgacctg 180
 cagccctaca aggagaggcc cagcgagaat gactccagct actgtctgag cagccggctg 240
 agggctctctg cctccttctg gcacaaccog cgcaaccact tccgtgcca agtccagttc 300
 tatgggctcg gggacgacga tgagtggaaa tacgatagag tcaaaccat caccagaac 360

atcagtgctg aggcctgggg cagagcagac tgtggcttca cctcgggtgc ctaccatcag 420
ggcgtcctgt ctgccaccat cctctatgag atcctgctgg gcaaggccac gctgtatgct 480
gtgctgggtca gcatectggt gctg 504

<210> 50

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 50

cgacaagacc caggtctgg

19

<210> 51

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 51

gtcagctccc aggacagag

19

<210> 52

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 52

catgacctgg gacatgggc

19

<210> 53

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 53

gagatgttcc cttatctctg g

21

<210> 54

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 54

cctctaacgt gggcaacag

19

<210> 55

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 55

tcagcagatc ccagcaaaag

20

<210> 56

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 56

agcaagacct caagcaactg

20

<210> 57

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 57

gtgaccttct gcagatcctc

20

<210> 58

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 58

agctcagctc cacgtggctc

19

<210> 59

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 59

tgctgaaccc actcgtgac

19

<210> 60

<211> 109

<212> PRT

<213> Canis familiaris

<220>

<223> At location 109, Xaa = Ala or Ser

<400> 60

Ile Gly Leu Leu Cys Gly Val Ala Phe Cys Phe Leu Gly Val Gly Leu
1 5 10 15Leu Asn Ala Gln Val Thr Gln Thr Pro Arg Gln Leu Ile Lys Lys Val
20 25 30

Gly Arg Lys Val Leu Leu Lys Cys Ser Gln Asn Met Asp His Glu Arg
 35 40 45

Trp Ser Tyr Asn Ile Asp Ser Val Glu Thr Gly Asp Ile Pro Tyr Gly
 50 55 60

Met Phe Trp Tyr Gln Gln Asp Pro Gly Leu Gly Leu Arg Leu Leu Tyr
 65 70 75 80

Tyr Ser Val Ser Arg Lys Lys Lys Asp Ala Phe Pro Leu Ile Leu Glu
 85 90 95

Ser Ala Arg Ile Asn Gln Thr Ser Val Tyr Phe Cys Xaa
 100 105

<210> 61

<211> 110

<212> PRT

<213> Canis familiaris

<220>

<223> At locations 109 and 110, Xaa =Ala or Ser

<400> 61

Ile Gly Leu Leu Cys Gly Val Ala Phe Cys Phe Leu Gly Val Gly Leu
 1 5 10 15

Leu Asn Ala Gln Val Thr Gln Thr Pro Arg Gln Leu Ile Lys Lys Val
 20 25 30

Gly Arg Lys Val Leu Leu Lys Cys Ser Gln Asn Met Asp His Glu Arg
 35 40 45

Trp Ser Tyr Asn Ile Asp Ser Val Glu Thr Gly Asp Ile Pro Tyr Gly
 50 55 60

Met Phe Trp Tyr Gln Gln Asp Pro Gly Leu Gly Leu Arg Leu Leu Tyr
 65 70 75 80

Tyr Ser Val Ser Arg Lys Lys Lys Asp Ala Phe Pro Leu Ile Leu Glu
 85 90 95

Ser Ala Arg Ile Asn Gln Thr Ser Val Tyr Phe Cys Xaa Xaa
 100 105 110

<210> 62

<211> 111

<212> PRT

<213> Canis familiaris

<220>

<223> At locations 109, 110 and 111, Xaa= Ala or Ser

<400> 62

Ile Gly Leu Leu Cys Gly Val Ala Phe Cys Phe Leu Gly Val Gly Leu
1 5 10 15

Leu Asn Ala Gln Val Thr Gln Thr Pro Arg Gln Leu Ile Lys Lys Val
20 25 30

Gly Arg Lys Val Leu Leu Lys Cys Ser Gln Asn Met Asp His Glu Arg
35 40 45

Trp Ser Tyr Asn Ile Asp Ser Val Glu Thr Gly Asp Ile Pro Tyr Gly
50 55 60

Met Phe Trp Tyr Gln Gln Asp Pro Gly Leu Gly Leu Arg Leu Leu Tyr
65 70 75 80

Tyr Ser Val Ser Arg Lys Lys Lys Asp Ala Phe Pro Leu Ile Leu Glu
85 90 95

Ser Ala Arg Ile Asn Gln Thr Ser Val Tyr Phe Cys Xaa Xaa Xaa
100 105 110

<210> 63

<211> 109

<212> PRT

<213> Canis familiaris

<220>

<223> At location 109, Xaa =Ala or Ser

<400> 63

Met Leu Thr Cys Leu Leu Leu Leu Leu Gly Gln Gly Ser Val Phe Gly
1 5 10 15

Ala Leu Val Ser Gln Lys Pro Arg Arg Asp Ile Cys Gln Arg Gly Thr
20 25 30

Ser Ile Thr Ile His Cys Glu Val Asp Thr Gln Val Thr Leu Met Phe
35 40 45

Trp Tyr Arg Gln Leu Pro Gly Gln Ser Leu Ile Leu Ile Ala Thr Ala
50 55 60

Ala Glu Ala Thr Tyr Glu Asn Gln Gly Ser Gly Phe Thr Arg Glu Lys
65 70 75 80

Phe Pro Ile Ser Arg Arg Thr Leu Met Phe Ser Thr Leu Thr Val Ser
 85 90 95

Asn Leu Ser Leu Glu Asp Thr Ser Ser Tyr Phe Cys Xaa
 100 105

<210> 64

<211> 110

<212> PRT

<213> Canis familiaris

<220>

<223> At locations 109 and 110, Xaa = Ala or Ser

<400> 64

Met Leu Thr Cys Leu Leu Leu Leu Leu Gly Gln Gly Ser Val Phe Gly
 1 5 10 15

Ala Leu Val Ser Gln Lys Pro Arg Arg Asp Ile Cys Gln Arg Gly Thr
 20 25 30

Ser Ile Thr Ile His Cys Glu Val Asp Thr Gln Val Thr Leu Met Phe
 35 40 45

Trp Tyr Arg Gln Leu Pro Gly Gln Ser Leu Ile Leu Ile Ala Thr Ala
 50 55 60

Ala Glu Ala Thr Tyr Glu Asn Gln Gly Ser Gly Phe Thr Arg Glu Lys
 65 70 75 80

Phe Pro Ile Ser Arg Arg Thr Leu Met Phe Ser Thr Leu Thr Val Ser
 85 90 95

Asn Leu Ser Leu Glu Asp Thr Ser Ser Tyr Phe Cys Xaa Xaa
 100 105 110

<210> 65

<211> 111

<212> PRT

<213> Canis familiaris

<220>

<223> At locations 109, 110 and 111, Xaa =Ala or Ser

<400> 65

Met Leu Thr Cys Leu Leu Leu Leu Leu Gly Gln Gly Ser Val Phe Gly
 1 5 10 15

Ala Leu Val Ser Gln Lys Pro Arg Arg Asp Ile Cys Gln Arg Gly Thr
 20 25 30

Ser Ile Thr Ile His Cys Glu Val Asp Thr Gln Val Thr Leu Met Phe
 35 40 45

Trp Tyr Arg Gln Leu Pro Gly Gln Ser Leu Ile Leu Ile Ala Thr Ala
 50 55 60

Ala Glu Ala Thr Tyr Glu Asn Gln Gly Ser Gly Phe Thr Arg Glu Lys
 65 70 75 80

Phe Pro Ile Ser Arg Arg Thr Leu Met Phe Ser Thr Leu Thr Val Ser
 85 90 95

Asn Leu Ser Leu Glu Asp Thr Ser Ser Tyr Phe Cys Xaa Xaa Xaa
 100 105 110

<210> 66

<211> 111

<212> PRT

<213> Canis familiaris

<220>

<223> At location 111, Xaa = Ala or Ser

<400> 66

Met Ala Thr Gly Val Phe Phe Gly Met Ala Leu Cys Val Leu Trp Thr
 1 5 10 15

Gly Tyr Met Asp Ala Gly Ile Ile Gln Ser Pro Arg Tyr Lys Val Thr
 20 25 30

Gly Thr Gly Lys Arg Val Thr Leu Arg Cys His Gln Thr Asp Asn Tyr
 35 40 45

Asp Tyr Met Tyr Trp Tyr Arg His Asp Leu Gly His Gly Pro Arg Leu
 50 55 60

Ile Tyr Tyr Ser Asn Gly Ile Asn Ser Thr Glu Lys Gly Asp Leu Ser
 65 70 75 80

Asn Gly Tyr Thr Val Ser Arg Ser Asn Lys Met Asp Phe Pro Leu Leu
 85 90 95

Leu Asp Ser Val Thr Ser Ser Gln Thr Ser Val Tyr Phe Cys Xaa
 100 105 110

<210> 67

<211> 112

<212> PRT

<213> Canis familiaris

<220>

<223> At locations 111 and 112, Xaa = Ala or Ser

<400> 67

```

Met Ala Thr Gly Val Phe Phe Gly Met Ala Leu Cys Val Leu Trp Thr
 1           5           10           15
Gly Tyr Met Asp Ala Gly Ile Ile Gln Ser Pro Arg Tyr Lys Val Thr
          20           25           30

Gly Thr Gly Lys Arg Val Thr Leu Arg Cys His Gln Thr Asp Asn Tyr
          35           40           45

Asp Tyr Met Tyr Trp Tyr Arg His Asp Leu Gly His Gly Pro Arg Leu
          50           55           60

Ile Tyr Tyr Ser Asn Gly Ile Asn Ser Thr Glu Lys Gly Asp Leu Ser
          65           70           75           80

Asn Gly Tyr Thr Val Ser Arg Ser Asn Lys Met Asp Phe Pro Leu Leu
          85           90           95

Leu Asp Ser Val Thr Ser Ser Gln Thr Ser Val Tyr Phe Cys Xaa Xaa
          100          105          110

```

<210> 68

<211> 113

<212> PRT

<213> Canis familiaris

<220>

<223> At locations 111, 112 and 113, Xaa = Ala or Ser

<400> 68

```

Met Ala Thr Gly Val Phe Phe Gly Met Ala Leu Cys Val Leu Trp Thr
 1           5           10           15

Gly Tyr Met Asp Ala Gly Ile Ile Gln Ser Pro Arg Tyr Lys Val Thr
          20           25           30

Gly Thr Gly Lys Arg Val Thr Leu Arg Cys His Gln Thr Asp Asn Tyr
          35           40           45

Asp Tyr Met Tyr Trp Tyr Arg His Asp Leu Gly His Gly Pro Arg Leu
          50           55           60

Ile Tyr Tyr Ser Asn Gly Ile Asn Ser Thr Glu Lys Gly Asp Leu Ser
          65           70           75           80

```

Xaa

<220>
<223> At location 111, Xaa = Ala or Ser

Leu Ile Gln Tyr Tyr Asn Arg Glu Glu Arg Asp Lys Gly Asp Ile Pro
65 70 75 80

Met Asn Ser Leu Glu Pro Gly Asp Ser Ala Leu Tyr Leu Cys Xaa
100 105 110

<220>
<223> At locations 111 and 112, Xaa = Ala or Ser

-40-


```

<220>
<223> At locations 111, 112 and 113, Xaa = Ala or Ser.
<400> 71
Met Gly Ser Arg Leu Leu Cys Cys Val Ala Leu Cys Leu Leu Gly Ala
 1         5             10             15

```

Met Asn Ser Leu Glu Pro Gly Asp Ser Ala Leu Tyr Leu Cys Xaa Xaa
100 105 110

-41-

<210> 72
 <211> 109
 <212> PRT
 <213> Canis familiaris

<220>
 <223> At location 109, Xaa = Ala or Ser

<400> 72
 Met Leu Met Leu Leu Leu Leu Gly Pro Ser Ser Gly Leu Gly Ala
 1 5 10 15
 Leu Val Phe Gln Ala Pro Ser Thr Met Ile Cys Lys Ser Gly Ala Thr
 20 25 30
 Val Gln Ile Gln Cys Gln Thr Val Asp Leu Gln Ala Thr Thr Val Phe
 35 40 45
 Trp Tyr Arg Gln Leu Pro Lys Gln Gly Leu Thr Leu Met Val Thr Ser
 50 55 60
 Asn Val Gly Asn Ser Ala Thr His Glu Gln Gly Phe Pro Ala Ala Lys
 65 70 75 80
 Phe Pro Val Asn His Pro Asn Leu Thr Phe Ser Ser Leu Met Val Thr
 85 90 95
 Ser Ser Gly Pro Gly Asp Ser Gly Leu Tyr Phe Cys Xaa
 100 105

<210> 73
 <211> 110
 <212> PRT
 <213> Canis familiaris

<220>
 <223> At location 109 and 110, Xaa = Ala or Ser

<400> 73
 Met Leu Met Leu Leu Leu Leu Gly Pro Ser Ser Gly Leu Gly Ala
 1 5 10 15
 Leu Val Phe Gln Ala Pro Ser Thr Met Ile Cys Lys Ser Gly Ala Thr
 20 25 30
 Val Gln Ile Gln Cys Gln Thr Val Asp Leu Gln Ala Thr Thr Val Phe
 35 40 45

Trp Tyr Arg Gln Leu Pro Lys Gln Gly Leu Thr Leu Met Val Thr Ser
 50 55 60

Asn Val Gly Asn Ser Ala Thr His Glu Gln Gly Phe Pro Ala Ala Lys
 65 70 75 80

Phe Pro Val Asn His Pro Asn Leu Thr Phe Ser Ser Leu Met Val Thr
 85 90 95

Ser Ser Gly Pro Gly Asp Ser Gly Leu Tyr Phe Cys Xaa Xaa
 100 105 110

<210> 74

<211> 111

<212> PRT

<213> Canis familiaris

<220>

<223> At locations 109, 110 and 111, Xaa = Ala or Ser

<400> 74

Met Leu Met Leu Leu Leu Leu Leu Gly Pro Ser Ser Gly Leu Gly Ala
 1 5 10 15

Leu Val Phe Gln Ala Pro Ser Thr Met Ile Cys Lys Ser Gly Ala Thr
 20 25 30

Val Gln Ile Gln Cys Gln Thr Val Asp Leu Gln Ala Thr Thr Val Phe
 35 40 45

Trp Tyr Arg Gln Leu Pro Lys Gln Gly Leu Thr Leu Met Val Thr Ser
 50 55 60

Asn Val Gly Asn Ser Ala Thr His Glu Gln Gly Phe Pro Ala Ala Lys
 65 70 75 80

Phe Pro Val Asn His Pro Asn Leu Thr Phe Ser Ser Leu Met Val Thr
 85 90 95

Ser Ser Gly Pro Gly Asp Ser Gly Leu Tyr Phe Cys Xaa Xaa Xaa
 100 105 110

<210> 75

<211> 112

<212> PRT

<213> Canis familiaris

<220>

<223> At location 112, Xaa = Ala or Ser

<400> 75

Met Cys Pro Val Phe Ile Cys Ser Leu Val Leu Trp Leu Leu Ser Thr
 1 5 10 15

Gly Thr Leu Asn Ala Lys Val Met Gln Thr Pro Gly His Leu Val Lys
 20 25 30

Gly Lys Gly Gln Lys Ala Lys Met Glu Cys Val Pro Ile Lys Gly His
 35 40 45

Ser Tyr Val Phe Trp Tyr Gln Gln Ile Pro Ala Lys Glu Phe Lys Phe
 50 55 60

Leu Ile Ser Phe Gln Asp Asn Ala Val Phe Asp Lys Thr Gly Met Pro
 65 70 75 80

Thr Gln Arg Phe Leu Ala Leu Cys Pro Lys Asn Leu Pro Cys Ser Leu
 85 90 95

Glu Ile Glu Arg Thr Glu Leu Gln Asp Ser Ala Val Tyr Phe Cys Xaa
 100 105 110

<210> 76

<211> 113

<212> PRT

<213> Canis familiaris

<220>

<223> At location 112 and 113, Xaa = Ala or Ser

<400> 76

Met Cys Pro Val Phe Ile Cys Ser Leu Val Leu Trp Leu Leu Ser Thr
 1 5 10 15

Gly Thr Leu Asn Ala Lys Val Met Gln Thr Pro Gly His Leu Val Lys
 20 25 30

Gly Lys Gly Gln Lys Ala Lys Met Glu Cys Val Pro Ile Lys Gly His
 35 40 45

Ser Tyr Val Phe Trp Tyr Gln Gln Ile Pro Ala Lys Glu Phe Lys Phe
 50 55 60

Leu Ile Ser Phe Gln Asp Asn Ala Val Phe Asp Lys Thr Gly Met Pro
 65 70 75 80

Thr Gln Arg Phe Leu Ala Leu Cys Pro Lys Asn Leu Pro Cys Ser Leu
 85 90 95

Glu Ile Glu Arg Thr Glu Leu Gln Asp Ser Ala Val Tyr Phe Cys Xaa

100

105

110

Xaa

<210> 77

<211> 114

<212> PRT

<213> Canis familiaris

<220>

<223> At location 112, 113 and 114, Xaa = Ala or Ser

<400> 77

Met Cys Pro Val Phe Ile Cys Ser Leu Val Leu Trp Leu Leu Ser Thr
 1 5 10 15

Gly Thr Leu Asn Ala Lys Val Met Gln Thr Pro Gly His Leu Val Lys
 20 25 30

Gly Lys Gly Gln Lys Ala Lys Met Glu Cys Val Pro Ile Lys Gly His
 35 40 45

Ser Tyr Val Phe Trp Tyr Gln Gln Ile Pro Ala Lys Glu Phe Lys Phe
 50 55 60

Leu Ile Ser Phe Gln Asp Asn Ala Val Phe Asp Lys Thr Gly Met Pro
 65 70 75 80

Thr Gln Arg Phe Leu Ala Leu Cys Pro Lys Asn Leu Pro Cys Ser Leu
 85 90 95

Glu Ile Glu Arg Thr Glu Leu Gln Asp Ser Ala Val Tyr Phe Cys Xaa
 100 105 110

Xaa Xaa

<210> 78

<211> 108

<212> PRT

<213> Canis familiaris

<220>

<223> At location 108, Xaa = Ala or Ser

<400> 78

Met Gly Ser Gly Phe Leu Cys Cys Met Val Leu Cys Leu Leu Gly Ala
 1 5 10 15

Ala Pro Leu Asp Thr Thr Val Ser Gln Thr Pro Arg Tyr Leu Ile Ala

20 25 30
 His Val Gly Ser Lys Lys Leu Leu Lys Cys Glu Gln Asn Leu Gly His
 35 40 45
 Asn Ala Met Tyr Trp Tyr Lys Gln Asp Leu Lys Gln Leu Leu Lys Ile
 50 55 60
 Met Phe Ile Tyr Phe Asn Gln Gly Leu Asn Leu Asn Glu Ser Val Pro
 65 70 75 80
 Gly Arg Phe Ser Pro Glu Thr Leu Thr Ser Ser Leu Thr Ser Cys Arg
 85 90 95
 Leu Leu Asn Ser Asp Ser Ala Val Tyr Phe Cys Xaa
 100 105

<210> 79
 <211> 109
 <212> PRT
 <213> Canis familiaris

<220>
 <223> At locations 108 and 109, Xaa = Ala or Ser

<400> 79
 Met Gly Ser Gly Phe Leu Cys Cys Met Val Leu Cys Leu Leu Gly Ala
 1 5 10 15
 Ala Pro Leu Asp Thr Thr Val Ser Gln Thr Pro Arg Tyr Leu Ile Ala
 20 25 30

His Val Gly Ser Lys Lys Leu Leu Lys Cys Glu Gln Asn Leu Gly His
 35 40 45
 Asn Ala Met Tyr Trp Tyr Lys Gln Asp Leu Lys Gln Leu Leu Lys Ile
 50 55 60
 Met Phe Ile Tyr Phe Asn Gln Gly Leu Asn Leu Asn Glu Ser Val Pro
 65 70 75 80
 Gly Arg Phe Ser Pro Glu Thr Leu Thr Ser Ser Leu Thr Ser Cys Arg
 85 90 95
 Leu Leu Asn Ser Asp Ser Ala Val Tyr Phe Cys Xaa Xaa
 100 105

<210> 80

<211> 110
 <212> PRT
 <213> Canis familiaris

<220>
 <223> At locations 108, 109 and 110, Xaa = Ala or Ser

<400> 80
 Met Gly Ser Gly Phe Leu Cys Cys Met Val Leu Cys Leu Leu Gly Ala
 1 5 10 15
 Ala Pro Leu Asp Thr Thr Val Ser Gln Thr Pro Arg Tyr Leu Ile Ala
 20 25 30
 His Val Gly Ser Lys Lys Leu Leu Lys Cys Glu Gln Asn Leu Gly His
 35 40 45
 Asn Ala Met Tyr Trp Tyr Lys Gln Asp Leu Lys Gln Leu Leu Lys Ile
 50 55 60
 Met Phe Ile Tyr Phe Asn Gln Gly Leu Asn Leu Asn Glu Ser Val Pro
 65 70 75 80
 Gly Arg Phe Ser Pro Glu Thr Leu Thr Ser Ser Leu Thr Ser Cys Arg
 85 90 95
 Leu Leu Asn Ser Asp Ser Ala Val Tyr Phe Cys Xaa Xaa Xaa
 100 105 110

<210> 81
 <211> 19
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 Primer

<220>
 <223> Y = T or C , R = G or A, N = A, C, G, or T

<400> 81
 ccgaattctg gtaycrnca

19

<210> 82
 <211> 18
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic

Primer

<220>

<223> R = G or A

<400> 82

cggatccgcr cartarta

18

<210> 83

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<220>

<223> R = G or A

<400> 83

cggatccgcr caraarta

18

<210> 84

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 84

ccagacctgg gtcttgctg

19

<210> 85

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 85

ctctgtcctg ggagctga

18

<210> 86
<211> 21
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 86
ttgtttgatc tagagactgt g

21

<210> 87
<211> 20
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 87
atcggactcc tctgtggtgt

20

<210> 88
<211> 20
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 88
acggtgaagg gctagcacct

20

<210> 89
<211> 20
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 89
gctgaaatgg ccaccggcgt

20

<210> 90
<211> 19
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 90
ctgttgccca cgtttagagg

19

<210> 91
<211> 19
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 91
ttactgaact gctgcactg

19

<210> 92
<211> 20
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 92
gctgcaggat tcggcacgag

20

<210> 93
<211> 20
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Primer

<400> 93
tacgactgtc agcttggtcc

20

<210> 94
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Primer

<400> 94
cttttgctgg gatctgctga

20

<210> 95
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Primer

<400> 95
cagttgctta ggtcttgct

19

<210> 96
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Primer

<400> 96
cacgagcctg ccatgtgccc

20

<210> 97
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Primer

<400> 97
ggcacgagca ctgaggacca

20

<400> 99

Met Gly Ser Arg Leu Leu Cys Cys Val Ala Leu Cys Leu Leu Gly Ala
 1 5 10 15

Gly Pro Val Glu Ser Glu Val Ile Gln Thr Pro Arg His Met Ile Lys
 20 25 30

Ala Arg Gly Gln Thr Val Thr Leu Arg Cys Ser Leu Ile Ser Gly His
 35 40 45

Leu Ser Val Tyr Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Arg Phe
 50 55 60

Leu Ile Gln Tyr Tyr Asn Arg Glu Glu Arg Asp Lys Gly Asp Ile Pro
 65 70 75 80

Ala Arg Phe Ser Val Gln Gln Phe Ser Asn Tyr Ser Ser Gln Leu Glu
 85 90 95

Met Asn Ser Leu Glu Pro Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
 100 105 110

Ser Leu Asp Ala Phe Asp Ala Gly Gln Leu Tyr Phe Gly Ala Gly Ser
 115 120 125

Lys Leu Ala Val Leu
 130

<210> 100

<211> 438

<212> DNA

<213> *Canis familiaris*

<400> 100

cagcacggcc agcttggaac cggccccgaa gtacagctgc cccgcgtcga acgcatctaa 60
 gctgctggca cagagatata gggctgagtc tcttggtcc agggagttca tctccagctg 120
 ggagctgtag ttactgaact gctgcactga gaatcttgcc gggatgtctc ctttgtctct 180
 ctcttccta ttgtaatact gaatgagaaa ccggggaccc tggcccaggg cctgttggtgta 240
 ccagtacaca gataggtgtc cagagataag ggaacatctc agggtcactg tctgtcctct 300
 tgctttgatc atgtgtcttg gagtttggat gacctcagac tccacggggc cggctcccag 360
 gagacaaagg gccacacagc agagaagcct ggagcccatg gcagccctgg gaagctgata 420
 gctccccgc tctctgtg 438

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 15/12, 15/62, 5/10, C07K 14/705, 16/28, C12Q 1/68, A61K 38/17, 31/70, 48/00	A3	(11) International Publication Number: WO 00/06733 (43) International Publication Date: 10 February 2000 (10.02.00)
(21) International Application Number: PCT/US99/17309 (22) International Filing Date: 29 July 1999 (29.07.99) (30) Priority Data: 60/094,506 29 July 1998 (29.07.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/094,506 (CIP) Filed on 29 July 1998 (29.07.98) (71) Applicant (for all designated States except US): HESKA CORPORATION [US/US]; 1825 Sharp Point Drive, Fort Collins, CO 80525 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): SIM, Gek-Kee [US/US]; 3622 Terry Point Drive, Fort Collins, CO 80524 (US). DREITZ, Matthew, J. [US/US]; 4324 Winterstone, Fort Collins, CO 80525 (US). (74) Agents: CONNELL, Gary, J. et al.; Sheridan Ross P.C., Suite 3500, 1700 Lincoln Street, Denver, CO 80203-4501 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 4 May 2000 (04.05.00)
(54) Title: T CELL RECEPTOR PROTEINS, NUCLEIC ACID MOLECULES, AND USES THEREOF		
(57) Abstract The present invention relates to TCR V β proteins; to TCR V β nucleic acid molecules, including those that encode such TCR V β proteins; to antibodies raised against such TCR V β proteins; and to therapeutic compounds that regulate TCR V β function. The present invention also includes methods to identify and obtain such proteins, nucleic acid molecules, antibodies, and inhibitory compounds. Also included in the present invention are therapeutic compositions comprising such proteins, nucleic acid molecules, antibodies and/or inhibitory compounds as well as the use of such therapeutic compositions to regulate an immune response in an animal. Also included in the present invention are methods to detect T cell expansion in an animal using reagents including, or derived from such proteins, nucleic acid molecules or antibodies.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/17309

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C12N15/62 C12N5/10 C07K14/705 C07K16/28
C12Q1/68 A61K38/17 A61K31/70 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K C12Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DATABASE GENBANK [Online] Accession No. AF082505, 6 January 1999 (1999-01-06) DREITZ M.J. & SIM G.K.: "T cell receptor beta chain hcvb3 (Canis familiaris)" XP002122470 the whole document	1-48
X	--- WO 92 12996 A (IMMUNE RESPONSE CORP INC) 6 August 1992 (1992-08-06) abstract figure 1 examples 1-13 claims 1-113	1-48
	--- -/-	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

16 November 1999

Date of mailing of the international search report

06.03.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Galli, I

INTERNATIONAL SEARCH REPORT

Inter- National Application No

PCT/US 99/17309

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WEDDERBURN L.R. ET AL.: "In vivo clonal dominance and limited T-cell receptor usage in human CD4+ T-cell recognition of house dust mite allergens" PROC. NATL. ACAD. SCI. USA, vol. 90, September 1993 (1993-09), pages 8214-8218, XP002122467 the whole document -& DATABASE GENBANK [Online] Accession No. Z23040, 17 January 1995 (1995-01-17) WEDDERBURN: "T-cell antigen receptor beta chain" XP002122471 compare seq. IDs 1 and 50 with nt 31-381 and 173-191, respectively</p>	1-48
A	<p>--- TAKANO M. ET AL.: "Identification of dog T-cell receptor beta chain genes" IMMUNOGENETICS, vol. 40, 1994, page 246 XP002122468 cited in the application the whole document</p>	1-48
A	<p>--- ITO K. ET AL.: "Isolation and sequence analysis of cDNA for the dog T-cell receptor Tcr-alpha and Tcr-beta chains" IMMUNOGENETICS, vol. 38, 1993, pages 60-63, XP002122469 cited in the application the whole document</p>	1-48
A	<p>--- US 5 635 354 A (KOURILSKY PHILIPPE ET AL) 3 June 1997 (1997-06-03) abstract -----</p>	1-48

INTERNATIONAL SEARCH REPORT

national application No.

PCT/US 99/ 17309

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 44,45
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-48 partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: (1-48) - partially

Isolated nCaV-beta3 polypeptide (seq. IDs 2,29,60,61,62) and homologs.

Corresponding nucleic acids (seq. IDs 1,28) and their allelic variants, complementary DNAs (Seq. ID 3,30), and a unique primer (Seq. ID 50).

Methods to detect expansion of T cells, therapeutic compositions, antibodies,kits.. Uses of said materials in therapeutic, diagnostic and detection applications.

2. Claims: (1-48) - partially

Idem as subject matter 1, but limited to mCaV-beta4 (Seq. IDs 5,32,63,64,65; 4,31,7; 6,33,8; 51)

3. Claims: (1-48) - partially

Idem as subject matter 1, but limited to mCaV-beta12 (Seq. IDs 10,35,66,67,68; 9,34,12; 11,36,13; 52)

4. Claims: (1-48) - partially

Idem as subject matter 1, but limited to mCaV-beta72 (seq. IDs 15,38,69,70,71,99; 37,98,17; 39,100,18; 53)

5. Claims: (3,6-9,20-48) - partially

Idem as subject matter 1, but limited to mCaV-beta21 (seq. IDs 20,72,73,74; 19; 54)

6. Claims: (3,6-9,20-48) - partially

Idem as subject matter 1, but limited to mCaV-beta54 (seq. IDs 23,75,76,77; 22; 24; 55)

7. Claims: (3,6-9,20-48) - partially

Idem as subject matter 1, but limited to mCaV-beta182 (seq. IDs 26,78,79,80; 25; 27; 56).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claim 9 (points i and vi) refer to mimetopes and inhibitors of the polypeptides without giving a true technical characterization. Moreover, no such compounds are defined in the characterization. In consequence, the scope of said claims is ambiguous and vague, and their subject-matter is not sufficiently disclosed and supported (Art. 5 and 6 PCT). No search can be carried out for such purely speculative claims whose wording is, in fact, a mere recitation of the results to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/17309

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9212996 A		06-08-1992	AU 1271692 A	27-08-1992
			AU 694062 B	09-07-1998
			AU 7032796 A	16-01-1997
			CA 2101065 A	23-07-1992
			EP 0568623 A	10-11-1993
			EP 0722738 A	24-07-1996
			JP 6507384 T	25-08-1994
			NO 932631 A	21-09-1993
			US 5985552 A	16-11-1999

US 5635354 A		03-06-1997	FR 2671356 A	10-07-1992
			CA 2100167 A	10-07-1992
			DE 69204823 D	19-10-1995
			DE 69204823 T	02-05-1996
			EP 0566685 A	27-10-1993
			ES 2079181 T	01-01-1996
			WO 9212260 A	23-07-1992
			JP 6508262 T	22-09-1994
